CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

Application Number : 074565

Trade Name : SELEGILINE HYDROCHLORIDE

Generic Name: Selegiline Hydrochloride Tablets 5mg

Sponsor : Endo Laboratories, Inc.

Approval Date: August 2, 1996

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION 074565

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CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 074565

APPROVAL LETTER

ANDA 74-565

AUG 2 1996

Endo Laboratories, L.L.C.
Attention: Carol Patterson
1000 Stewart Avenue
Garden City, NY 11530

Dear Madam:

This is in reference to your abbreviated new drug application dated August 23, 1994, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act, for Selegiline Hydrochloride Tablets USP, 5 mg.

Reference is also made to your amendments dated April 4 and 23, 1996 and June 18, 1996.

We have completed the review of this abbreviated application and have concluded that the drug is safe and effective for use as recommended in the submitted labeling. Accordingly, the application is approved. The Division of Bioequivalence has determined your Selegiline Hydrochloride Tablets USP, 5 mg to be bioequivalent and, therefore, therapeutically equivalent to the listed drug Eldepryl Tablets, 5 mg of Somerset Pharmaceuticals, Inc. Your dissolution testing should be incorporated into the stability and quality control program using the same method proposed in your application.

Under 21 CFR 314.70, certain changes in the conditions described in this abbreviated application require an approved supplemental application before the change may be made.

Post-marketing reporting requirements for this abbreviated application are set forth in 21 CFR 314.80-81. The Office of Generic Drugs should be advised of any change in the marketing status of this drug.

We request that you submit, in duplicate, any proposed advertising or promotional copy which you intend to use in your initial advertising or promotional campaigns. Please submit all proposed materials in draft or mock-up form, not final print. Submit both copies together with a copy of the proposed or final printed labeling to the Division of Drug Marketing, Advertising, and Communications (HFD-240). Please do not use Form FD-2253 (Transmittal of Advertisements and Promotional Labeling for Drugs for Human Use) for this initial submission.

We call your attention to 21 CFR 314.81(b)(3) which requires that materials for any subsequent advertising or promotional campaign be submitted to our Division of Drug Marketing, Advertising, and Communications (HFD-240) with a completed Form FD-2253 at the time of their initial use.

Sincerely yours,

D. L. Sporn 8/2/96

Douglas L. Sporn
Director
Office of Generic Drugs
Center for Drug Evaluation and Research

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER 074565

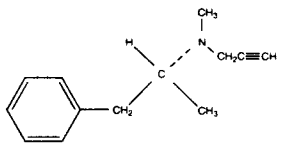
FINAL PRINTED LABELING

Endo

SELEGILINE HYDROCHLORIDE TABLETS, USP

DESCRIPTION:
Selegiline hydrochloride is a levorotatory acetylenic derivative of phenethylamine. It is commonly referred to in the clinical and pharmacological literature as L-deprenyl.

The chemical name is: (R)-(-)-N,2-dimethyl-N-2-propynylphenethylamine hydrochloride. It is a white to near white crystalline powder, freely soluble in water, chloroform, and methanol. The molecular formula is $C_{13}H_{17}N \cdot HCl$; and the molecular weight is 223.75. The structural formula is as follows:



Each tablet, for oral administration contains selegiline hydrochloride, 5 mg and the following inactive ingredients: corn starch, lactose monohydrate, magnesium stearate, povidone, and talc.

CLINICAL PHARMACOLOGY:
The mechanisms accounting for selegiline's beneficial adjunctive action in the treatment of Parkinson's disease are not fully understood. Inhibition of monoamine oxidase, type B, activity is generally considered to be of primary importance; in addition, there is evidence that selegiline may act through other mechanisms to increase dopaminergic activity.

Selegiline is best known as an irreversible inhibitor of monoamine oxidase (MAO), an intracellular enzyme associated with the outer membrane of mitochondria. Selegiline inhibits MAO by acting as a 'suicide' substrate for the enzyme; that is, it is converted by MAO to an active moiety which combines irreversibly with the active site and/or the enzyme's essential FAD cofactor. Because selegiline has greater affinity for type B than for Type A active sites, it can serve as a selective inhibitor of MAO type B if it is administered at the recommended dose.

MAOs are widely distributed throughout the body; their concentration is especially high in liver, kidney, stomach, intestinal wall, and brain. MAOs are currently subclassified into two types, A and B, which differ in their substrate specificity and tissue distribution. In humans, intestinal MAO is predominantly type A, while most of that in brain is type B.

In CNS neurons, MAO plays an important role in the catabolism of catecholamines (dopamine, norepinephrine and epinephrine) and serotonin. MAOs are also important in the catabolism of various exogenous amines found in a variety of foods and drugs. MAO in the GI tract and liver (primarily type A), for example, is thought to provide vital protection from exogenous amines (e.g., tyramine) that have the capacity, if absorbed intact, to cause a 'hypertensive crisis,' the so-called 'cheese reaction.' (If large amounts of certain exogenous amines gain access to the systemic circulation - e.g., from fermented cheese, red wine, herring, over-the-counter cough/cold medications, etc. - they are taken up by adrenergic neurons and displace norepinephrine from storage sites within membrane bound vesicles. Subsequent release of the displaced norepinephrine causes the rise in systemic blood pressure, etc.)

In theory, therefore, because MAO A of the gut is not inhibited, patients treated with selegiline at a dose of 10 mg a day can take medications containing pharmacologically active amines and consume tyramine-containing foods without risk of uncontrolled hypertension. However, one case of hypertensive crisis has been reported in a patient taking the recommended dose of selegiline and a sympathomimetic medication (ephedrine). The pathophysiology of the 'cheese reaction' is complicated and, in addition to its ability to inhibit MAO B selectively, selegiline's relative freedom from this reaction has been attributed to an ability to prevent tyramine and other indirect acting sympathomimetics from displacing norepinephrine from adrenergic neurons.

However, until the pathophysiology of the cheese reaction is more completely understood, it seems prudent to assume that selegiline can only be used safely without dietary restrictions at doses where it presumably selectively inhibits MAO B (e.g., 10 mg/day). **In short, attention to the dose dependent nature of selegiline's selectivity is critical if it is to be used without elaborate restrictions being placed on diet and concomitant drug use although, as noted above, a case of hypertensive crisis has been reported at the recommended dose. (See WARNINGS and PRECAUTIONS.)**

It is important to be aware that selegiline may have pharmacological effects unrelated to MAO B inhibition. As noted above, there is some evidence that it may increase dopaminergic activity by other mechanisms, including interfering with dopamine re-uptake at the synapse. Effects resulting from selegiline administration may also be mediated through its metabolites. Two of its three principal metabolites, amphetamine and methamphetamine, have pharmacological actions of their own; they interfere with neuronal uptake and enhance release of several neurotransmitters (e.g., norepinephrine, dopamine, serotonin). However, the extent to which these metabolites contribute to the effects of selegiline are unknown.

Rationale for the Use of a Selective Monoamine Oxidase Type B Inhibitor in Parkinson's Disease:
Many of the prominent symptoms of Parkinson's disease are due to a deficiency of striatal dopamine that is the consequence of a progressive degeneration and loss of a population of dopaminergic neurons which originate in the substantia nigra of the midbrain and project to the basal ganglia or striatum. Early in the course of Parkinson's Disease, the deficit in the capacity of these neurons to synthesize dopamine can be overcome by administration of exogenous levodopa, usually given in combination with a peripheral decarboxylase inhibitor (carbidopa).

With the passage of time, due to the progression of the disease and/or the effect of sustained treatment, the efficacy and quality of the therapeutic response to levodopa diminishes. Thus, after several years of levodopa treatment, the response, for a given dose of levodopa, is shorter, has less predictable onset and offset (i.e., there is 'wearing off'), and is often accompanied by side effects (e.g., dyskinesia, akinesias, on-off phenomena, freezing, etc.)

This deteriorating response is currently interpreted as a manifestation of the inability of the ever decreasing population of intact nigrostriatal neurons to synthesize and release adequate amounts of dopamine.

MAO B inhibition may be useful in this setting because, by blocking the catabolism of dopamine, it would increase the net amount of dopamine available (i.e., it would increase the pool of dopamine). Whether or not this mechanism or an alternative one actually accounts for the observed beneficial effects of adjunctive selegiline is unknown.

Selegiline's benefit in Parkinson's disease has only been documented as an adjunct to levodopa/carbidopa. Whether or not it might be effective as a sole treatment is unknown, but past attempts to treat Parkinson's disease with non-selective MAOI monotherapy are reported to have been unsuccessful. It is important to note that attempts to treat Parkinsonian patients with combinations of levodopa and currently marketed non-selective MAO inhibitors were abandoned because of multiple side effects including hypertension, increase in involuntary movement, and toxic delirium.

Pharmacokinetic Information (Absorption, Distribution, Metabolism and Elimination – ADME):
Only preliminary information about the details of the pharmacokinetics of selegiline and its metabolites is available.

Data obtained in a study of 12 healthy subjects that was intended to examine the effects of selegiline on the ADME of an oral hypoglycemic agent, however, provides some information. Following the oral administration of a single dose of 10 mg of selegiline hydrochloride to these subjects, serum levels of intact selegiline were below the limit of detection (less than 10 ng/mL). Three metabolites, N-desmethyldeprenyl, the major metabolite (mean half-life 2.0 hours), amphetamine (mean half-life 17.7 hours), and methamphetamine (mean half-life 20.5 hours), were found in serum and urine. Over a period of 48 hours, 45% of the dose administered appeared in the urine as these 3 metabolites.

In an extension of this study intended to examine the effects of steady state conditions, the same subjects were given a 10 mg dose of selegiline hydrochloride for seven consecutive days. Under these conditions, the mean trough serum levels for amphetamine were 3.5 ng/mL and 8.0 ng/mL for methamphetamine; trough levels of N-desmethyldeprenyl were below the levels of detection.

The rate of MAO B regeneration following discontinuation of treatment has not been quantitated. It is this rate, dependent upon de novo protein synthesis, which seems likely to determine how fast normal MAO B activity can be restored.

INDICATIONS AND USAGE:
Selegiline hydrochloride is indicated as an adjunct in the management of Parkinsonian patients being treated with levodopa/carbidopa who exhibit deterioration in the quality of their response to this therapy. There is no evidence from controlled studies that selegiline has any beneficial effect in the absence of concurrent levodopa therapy.

Evidence supporting this claim was obtained in randomized controlled clinical investigations that compared the effects of added selegiline or placebo in patients receiving levodopa/carbidopa. Selegiline was significantly superior to placebo on all three principal outcome measures employed: change from baseline in daily levodopa/carbidopa dose, the amount of 'off' time, and patient self-rating of treatment success. Beneficial effects were also observed on other measures of treatment success (e.g., measures of reduced end of dose akinesia, decreased tremor and sialorrhea, improved speech and dressing ability and improved overall disability as assessed by walking and comparison to previous state).

CONTRAINDICATIONS:
Selegiline hydrochloride is contraindicated in patients with a known hypersensitivity to this drug.

Selegiline hydrochloride is contraindicated for use with meperidine. This contraindication is often extended to other opioids. (See **Drug Interactions.**)

WARNINGS:
Selegiline should not be used at daily doses exceeding those recommended (10 mg/day) because of the risks associated with non-selective inhibition of MAO. (See CLINICAL PHARMACOLOGY.)

The selectivity of selegiline for MAO B may not be absolute even at the recommended daily dose of 10 mg a day and selectivity is further diminished with increasing daily doses. The precise dose at which selegiline becomes a non-selective inhibitor of all MAO is unknown, but may be in the range of 30 to 40 mg a day.

Severe CNS toxicity associated with hyperpyrexia and death have been reported with the combination of tricyclic antidepressants and non-selective MAOIs (Phenelzine, Tranylcypromine). A similar reaction has been reported for a patient on amitriptyline and selegiline. Another patient receiving protriptyline and selegiline developed tremors, agitation, and restlessness followed by unresponsiveness and death two weeks after selegiline was added. Related adverse events including hypertension, syncope, asystole, diaphoresis, seizures, changes in behavioral and mental status, and muscular rigidity have also been reported in some patients receiving selegiline and various tricyclic antidepressants.

Serious, sometimes fatal, reactions with signs and symptoms that may include hyperthermia, rigidity, myoclonus, autonomic instability with rapid fluctuations of the vital signs, and mental status changes that include extreme agitation progressing to delirium and coma have been reported with patients receiving a combination of fluoxetine hydrochloride and non-selective MAOIs. Similar signs have been reported in some patients on the combination of selegiline (10 mg a day) and selective serotonin reuptake inhibitors including fluoxetine, sertraline and paroxetine.

Since the mechanisms of these reactions are not fully understood, it seems prudent, in general, to avoid this combination of selegiline and tricyclic antidepressants as well as selegiline and selective serotonin reuptake inhibitors. At least 14 days should elapse between discontinuation of selegiline and initiation of treatment with a tricyclic antidepressant or selective serotonin reuptake inhibitors. Because of the long half lives of fluoxetine and its active metabolite, at least five weeks (perhaps longer, especially if fluoxetine has been prescribed chronically and/or at higher doses) should elapse between discontinuation of fluoxetine and initiation of treatment with selegiline.

PRECAUTIONS:
General:
Some patients given selegiline may experience an exacerbation of levodopa associated side effects, presumably due to the increased amounts of dopamine reaction with super-sensitive post-synaptic receptors. These effects may often be mitigated by reducing the dose of levodopa/carbidopa by approximately 10 to 30%.

The decision to prescribe selegiline should take into consideration that the MAO system of enzymes is complex and incompletely understood and there is only a limited amount of carefully documented clinical experience with selegiline. Consequently, the full spectrum of possible responses to selegiline may not have been observed in pre-marketing evaluation of the drug. It is advisable, therefore, to observe patients closely for atypical responses.

Information for Patients:
Patients should be advised of the possible need to reduce levodopa dosage after the initiation of selegiline hydrochloride therapy.

Patients (or their families if the patient is incompetent) should be advised not to exceed the daily recommended dose of 10 mg. The risk of using higher daily doses of selegiline should be explained, and a brief description of the 'cheese reaction' provided. While hypertensive reactions with selegiline associated with dietary influences have not been reported, documented experience is limited.

Consequently, it may be useful to inform patients (or their families) about the signs and symptoms associated with MAOI induced hypertensive reactions. In particular, patients should be urged to report, immediately, any severe headache or other atypical or unusual symptoms not previously experienced.

Laboratory Tests:
No specific laboratory tests are deemed essential for the management of patients on selegiline hydrochloride. Periodic routine evaluation of all patients, however, is appropriate.

Drug Interactions:
The occurrence of stupor, muscular rigidity, severe agitation, and elevated temperature has been reported in some patients receiving the combination of selegiline and meperidine. Symptoms usually resolve over days when the combination is discontinued. This is typical of the interaction of meperidine and MAOIs. Other serious reactions (including severe agitation, hallucinations, and death) have been reported in patients receiving this combination (see **CONTRAINDICATIONS**). Severe toxicity has also been reported in patients receiving the combination of tricyclic antidepressants and selegiline and selective serotonin reuptake inhibitors and selegiline. (See **WARNINGS** for details). One case of hypertensive crisis has been reported in a patient taking the recommended doses of selegiline and a sympathomimetic medication (ephedrine).

Carcinogenesis, Mutagenesis, and Impairment of Fertility:
Assessment of the carcinogenic potential of selegiline in mice and rats is ongoing.

Selegiline did not induce mutations or chromosomal damage when tested in the bacterial mutation assay in *Salmonella typhimurium* and an *in vivo* chromosomal aberration assay. While these studies provide some reassurance that selegiline is not mutagenic or clastogenic, they are not definitive because of methodological limitations. No definitive *in vitro* chromosomal aberration or in vitro mammalian gene mutation assays have been performed.

The effect of selegiline on fertility has not been adequately assessed.

Pregnancy:
Pregnancy, Teratogenic Effects, Pregnancy Category C. No teratogenic effects were observed in a study of embryo-fetal development in Sprague-Dawley rats at oral doses of 4, 12, and 36 mg/kg or 4, 12 and 35 times the human therapeutic dose on a mg/m^2 basis. No teratogenic effects were observed in a study of embryo-fetal development in New Zealand White rabbits at oral doses of 5, 25, and 50 mg/kg or 10, 48, and 95 times the human therapeutic dose on a mg/m^2 basis; however, in this study, the number of litters produced at the two higher doses was less than recommended for assessing teratogenic potential. In the rat study, there was a decrease in fetal body weight at the highest dose tested. In the rabbit study, increases in total resorptions and % post-implantation loss, and a decrease in the number of live fetuses per dam occurred at the highest dose tested. In a peri- and postnatal development study in Sprague-Dawley rats (oral doses of 4, 16, and 64 mg/kg or 4, 15, and 62 times the human therapeutic dose on a mg/m^2 basis), an increase in the number of stillbirths and decreases in the number of pups per dam, pup survival, and pup body weight (at birth and throughout the lactation period) were observed at the two highest doses. At the highest dose tested, no pups born alive survived to Day 4 postpartum. Postnatal development at the highest dose tested in dams could not be evaluated because of the lack of surviving pups. The reproductive performance of the untreated offspring was not assessed.

There are no adequate and well-controlled studies in pregnant women. Selegiline should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers:
It is not known whether selegiline hydrochloride is excreted in human milk. Because many drugs are excreted in human milk, consideration should be given to discontinuing the use of all but absolutely essential drug treatments in nursing women.

Pediatric Use:
The effects of selegiline hydrochloride in pediatric patients have not been evaluated.

ADVERSE REACTIONS:
Introduction:
The number of patients who received selegiline in prospectively monitored pre-marketing studies is limited. While other sources of information about the use of selegiline are available (e.g., literature reports, foreign post-marketing reports, etc.) they do not provide the kind of information necessary to estimate the incidence of adverse events. Thus, overall incidence figures for adverse reactions associated with the use of selegiline cannot be provided. Many of the adverse reactions seen have also been reported as symptoms of dopamine excess.

Moreover, the importance and severity of various reactions reported often cannot be ascertained. One index of relative importance, however, is whether or not a reaction caused treatment discontinuation. In prospective pre-marketing studies, the following events led, in decreasing order of frequency, to discontinuation of treatment with selegiline: nausea, hallucinations, confusion, depression, loss of balance, insomnia, orthostatic hypotension, increased akinetic involuntary movements, agitation, arrhythmia, bradykinesia, chorea, delusions, hypertension, new or increased angina pectoris and syncope. Events reported only once as a cause of discontinuation are ankle edema, anxiety, burning lips/mouth, constipation, drowsiness/lethargy, dystonia, excess perspiration, increased freezing, gastrointestinal bleeding, hair loss, increased tremor, nervousness, weakness and weight loss.

Experience with selegiline hydrochloride obtained in parallel, placebo controlled, randomized studies provides only a limited basis for estimates of adverse reaction rates. The following reactions that occurred with greater frequency among the 49 patients assigned to selegiline as compared to the 50 patients assigned to placebo in the only parallel, placebo controlled trial performed in patients with Parkinson's disease are shown in the following Table. None of these adverse reactions led to a discontinuation of treatment.

INCIDENCE OF TREATMENT-EMERGENT ADVERSE EXPERIENCES IN THE PLACEBO-CONTROLLED CLINICAL TRIAL

Adverse Event	Number of Patients Reporting Events	
	selegiline hydrochloride N=49	placebo N=50
Nausea	10	3
Dizziness/Lightheaded/Fainting	7	1
Abdominal Pain	4	2
Confusion	3	0
Hallucinations	3	1
Dry mouth	3	1
Vivid Dreams	2	0
Dyskinesias	2	5
Headache	2	1

INCIDENCE OF TREATMENT-EMERGENT ADVERSE EXPERIENCES IN THE PLACEBO-CONTROLLED CLINICAL TRIAL (cont'd.)

Adverse Event	Number of Patients Reporting Events	
	selegiline hydrochloride N=49	placebo N=50
The following events were reported once in either or both groups:		
Ache, generalized	1	0
Anxiety/Tension	1	1
Anemia	0	1
Diarrhea	1	0
Hair Loss	0	1
Insomnia	1	1
Lethargy	1	0
Leg pain	1	0
Low back pain	1	0
Malaise	0	1
Palpitations	1	0
Urinary Retention	1	0
Weight Loss	1	0

In all prospectively monitored clinical investigations, enrolling approximately 920 patients, the following adverse events, classified by body system, were reported.

Central Nervous System:
Motor/Coordination/Extrapyramidal:
increased tremor, chorea, loss of balance, restlessness, blepharospasm, increased bradykinesia, facial grimace, falling down, heavy leg, muscle twitch*, myoclonic jerks*, stiff neck, tardive dyskinesia, dystonic symptoms, dyskinesia, involuntary movements, freezing, festination, increased apraxia, muscle cramps.

Mental Status/Behavioral/Psychiatric:
hallucinations, dizziness, confusion, anxiety, depression, drowsiness, behavior/mood change, dreams/nightmares, tiredness, delusions, disorientation, lightheadedness, impaired memory*, increased energy*, transient high*, hollow feeling, lethargy/malaise, apathy, overstimulation, vertigo, personality change, sleep disturbance, restlessness, weakness, transient irritability.

Pain/Altered Sensation:
headache, back pain, leg pain, tinnitus, migraine, supraorbital pain, throat burning, generalized ache, chills, numbness of toes/fingers, taste disturbance.

Autonomic Nervous System:
dry mouth, blurred vision, sexual dysfunction.

Cardiovascular:
orthostatic hypotension, hypertension, arrhythmia, palpitations, new or increased angina pectoris, hypotension, tachycardia, peripheral edema, sinus bradycardia, syncope.

Gastrointestinal:
nausea/vomiting, constipation, weight loss, anorexia, poor appetite, dysphagia, diarrhea, heartburn, rectal bleeding, bruxism*, gastrointestinal bleeding (exacerbation of preexisting ulcer disease).

Genitourinary/Gynecologic/Endocrine:
slow urination, transient anorgasmia*, nocturia, prostatic hypertrophy, urinary hesitancy, urinary retention, decreased penile sensation*, urinary frequency.

Skin and Appendages:
increased sweating, diaphoresis, facial hair, hair loss, hematoma, rash, photosensitivity.

Miscellaneous:
asthma, diplopia, shortness of breath, speech affected.

Postmarketing Reports:
The following experiences were described in spontaneous post-marketing reports. These reports do not provide sufficient information to establish a clear causal relationship with the use of selegiline hydrochloride.

CNS:
Seizure in dialyzed chronic renal failure patient on concomitant medications.

* indicates events reported only at doses greater than 10 mg/day.

OVERDOSAGE:
Selegiline:
No specific information is available about clinically significant overdoses with selegiline hydrochloride. However, experience gained during selegiline's development reveals that some individuals exposed to doses of 600 mg d,l selegiline suffered severe hypotension and psychomotor agitation.

Since the selective inhibition of MAO B by selegiline hydrochloride is achieved only at doses in the range recommended for the treatment of Parkinson's disease (e.g., 10 mg/day), overdoses are likely to cause significant inhibition of both MAO A and MAO B. Consequently, the signs and symptoms of overdose may resemble those observed with marketed non-selective MAO inhibitors [e.g., tranylcypromine, isocarboxazide, and phenelzine].

Overdose with Non-Selective MAO Inhibition:
NOTE: This section is provided for reference; it does not describe events that have actually been observed with selegiline in overdose.

Characteristically, signs and symptoms of non-selective MAOI overdose may not appear immediately. Delays of up to 12 hours between ingestion of drug and the appearance of signs may occur. Importantly, the peak intensity of the syndrome may not be reached for upwards of a day following the overdose. Death has been reported following overdosage. Therefore, immediate hospitalization, with continuous patient observation and monitoring for a period of at least two days following the ingestion of such drugs in overdose, is strongly recommended.

The clinical picture of MAOI overdose varies considerably; its severity may be a function of the amount of drug consumed. The central nervous and cardiovascular systems are prominently involved.

Signs and symptoms of overdosage may include, alone or in combination, any of the following: drowsiness, dizziness, faintness, irritability, hyperactivity, agitation, severe headache, hallucinations, trismus, opisthotonos, convulsions, and coma; rapid and irregular pulse, hypertension, hypotension and vascular collapse; precordial pain, respiratory depression and failure, hyperpyrexia, diaphoresis, and cool, clammy skin.

Treatment Suggestions For Overdose:
NOTE: Because there is no recorded experience with selegiline overdose, the following suggestions are offered based upon the assumption that selegiline overdose may be modeled by non-selective MAOI poisoning. In any case, up-to-date information about the treatment of overdose can often be obtained from a certified Regional Poison Control Center. Telephone numbers of certified Poison Control Centers are listed in the Physicians' Desk Reference (PDR).

Treatment of overdose with non-selective MAOIs is symptomatic and supportive. Induction of emesis or gastric lavage with instillation of charcoal slurry may be helpful in early poisoning, provided the airway has been protected against aspiration. Signs and symptoms of central nervous system stimulation, including convulsions, should be treated with diazepam, given slowly intravenously. Phenothiazine derivatives and central nervous system stimulants should be avoided. Hypotension and vascular collapse should be treated with intravenous fluids and, if necessary, blood pressure titration with an intravenous infusion of a dilute pressor agent. It should be noted that adrenergic agents may produce a markedly increased pressor response.

Respiration should be supported by appropriate measures, including management of the airway, use of supplemental oxygen, and mechanical ventilatory assistance, as required.

Body temperature should be monitored closely. Intensive management of hyperpyrexia may be required. Maintenance of fluid and electrolyte balance is essential.

DOSAGE AND ADMINISTRATION:
Selegiline hydrochloride is intended for administration to Parkinsonian patients receiving levodopa/carbidopa therapy who demonstrate a deteriorating response to this treatment. The recommended regimen for the administration of selegiline hydrochloride is 10 mg per day administered as divided doses of 5 mg each taken at breakfast and lunch. There is no evidence that additional benefit will be obtained from the administration of higher doses. Moreover, higher doses should ordinarily be avoided because of the increased risk of side effects.

After two to three days of selegiline treatment, an attempt may be made to reduce the dose of levodopa/carbidopa. A reduction of 10 to 30% was achieved with the typical participant on the domestic placebo controlled trials who was assigned to selegiline treatment. Further reductions of levodopa/carbidopa may be possible during continued selegiline therapy.

HOW SUPPLIED:

Selegiline Hydrochloride Tablets, USP are supplied as follows:

5 mg – white, oval tablets; debossed with E620 on one side and plain on the other.

Bottles of 60	NDC 60951-620-60
Bottles of 500	NDC 60951-620-85

Store at controlled room temperature, 15°-30°C (59°-86°F). Dispense in a tight, light-resistant container, as defined in the USP, with a child-resistant closure (as required).

Caution: Federal (USA) law prohibits dispensing without prescription.

Manufactured for:
Endo Laboratories, L.L.C.
Wilmington, Delaware 19880

By:
DuPont Pharma
Wilmington, Delaware 19880

6383/June, 1996

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER 074565

CHEMISTRY REVIEW(S)

JUL 18 1996

Selegiline Hydrochloride Tablets
5 mg Tablet
ANDA #74-565
Reviewer: Moo Park
Filename: 74565A.N95

Endo Labs
Garden City, New York
Submission Date:
November 27, 1995

Review of an Amendment

I. Objective

Review of Endo's response to deficiency letter issued on 10/30/95.

II. Background

Two in vivo bioequivalence studies under fasting and non-fasting conditions were originally submitted on 11/10/94 and an amendment was submitted on 4/20/95. The review of the studies were completed as of 8/31/95 and deficiency letter was issued as of 10/30/95. Summary of PK parameters and statistical analyses was attached as reference.

Endo was informed of the following deficiencies:

1. Concentrations of the internal standard under recovery data for the parent drug and metabolites should be identified.

2. Room temperature stability for metabolites: Storage time is missing.

3. Submitted C_{max} data on a PC diskette are different from the data in hard copy for amphetamine under food conditions.

4. Some of the SAS analysis output were compiled out of order and it causes difficulty reviewing. Care should be taken for future submissions.

5. For future submission of dissolution data, range (high and low) should be reported in addition to the mean, sd, and %CV.

III. Review of Endo's response

1. Concentration of the internal standard under recovery data:

2. Storage time for stability samples at room temperature

3. PC data diskette: The firm explained that formatting of the data (CMAX of amphetamine) was the reason for the discrepancy.

4. The firm acknowledged deficiencies #4 and 5 concerning the presentation of SAS data and dissolution data. They will correct the deficiencies in the future submissions.

5. Endo's responses to the deficiencies #1-5 are acceptable.

IV. Comments

1. PK parameters for selegiline (parent drug) under fasting conditions: The test/reference ratios (as antilogs) for the log-transformed AUCT, AUCI and CMAX are all within acceptable range of 0.8-1.25.

2. Results of *in vivo* bioequivalence studies under fasting and nonfasting conditions for the parent drug and metabolites met the Agency requirements for bioequivalency as summarized in the earlier review (review date: 8/31/95) and in pp.4-8.

V. Recommendations

1. The *in vivo* bioequivalence studies conducted by Endo Laboratories under fasting and non-fasting conditions comparing its Selegiline Hydrochloride Tablets, 5 mg strength, lot #FE067A, to Somerset Pharmaceuticals' Eldepryl^{R}, 5 mg strength, lot #3Z011D, have been found acceptable by the Division of Bioequivalence. The studies demonstrated that Endo's Selegiline Hydrochloride Tablets, 5 mg strength, is bioequivalent to the reference product, Somerset Pharmaceuticals' Eldepryl^{R}, 5 mg strength.

2. The dissolution testing conducted by Endo Laboratories on its Selegiline Hydrochloride Tablets, 5 mg strength, Lot # FE067A, is acceptable.

3. The dissolution testing should be conducted on 12 units of the product in 500 mL of water at 37°C using USP 23 apparatus 2 (paddle) at 50 rpm. The test product should meet the following specifications:

   Not less than of the labeled amount of the drug in the dosage form is dissolved in 30 minutes.

4. From the bioequivalence point of view, the firm has met the *in vivo* and *in vitro* bioequivalence requirements and the submission is approvable.

The firm should be informed of the recommendations.

Moo Park, Ph.D.
Review Branch III

SUMMARY OF ANDA #74-565:

The data tables used in the summary were copied from the text of the original review (review date:8/31/96) and the table No's were left unchanged for easier referencing.

I. Fasting studies

Table 11. TEST MEAN/REFERENCE MEAN RATIOS (*ANTILOG CONVERSION) For Selegiline

	MEAN1	SD1	MEAN2	SD2	RMEAN12
PARAMETER					
AUCI	749.89	1418.16	532.78	580.68	1.41
AUCT	618.41	1280.54	445.63	541.40	1.39
CMAX	684.97	1101.17	644.69	811.31	1.06
LAUCI*	346.37	1.07	356.64	0.87	0.97
LAUCT*	262.19	1.11	272.01	0.97	0.96
LCMAX*	358.01	1.01	398.57	0.96	0.90

UNIT: AUC=PG HR/ML CMAX=PG/ML TMAX=HR

Table 12. LSMEANS AND 90% CONFIDENCE INTERVALS FOR SELEGILINE

	LSMEAN1	LSMEAN2	LOWCI12	UPPCI12
PARAMETER				
AUCI	695.42	407.07	70.94	270.73
AUCT	632.72	444.25	75.17	209.67
CMAX	698.70	645.92	78.60	137.75
LAUCI	310.10	322.75	84.28	109.53
LAUCT	266.59	270.30	85.42	113.87
LCMAX	363.17	396.66	78.09	107.35

LSMEAN1=LSMEAN FOR THE TEST PRODUCT
LSMEAN2=LSMEAN FOR THE REFERENCE PRODUCT

Table 17. LSMEANS AND 90% CONFIDENCE INTERVALS FOR AMPHETAMINE

PARAMETER	LSMEAN1	LSMEAN2	LOWCI12	UPPCI12
AUCI	91.39	96.01	91.25	99.12
AUCT	77.61	82.30	89.06	99.54
CMAX	2.89	2.92	93.26	104.24
LAUCI	88.76	93.72	90.95	98.63
LAUCT	74.65	79.73	88.08	99.54
LCMAX	2.81	2.88	92.76	102.98

Table 22. LSMEANS AND 90% CONFIDENCE INTERVALS FOR METHAMPHETAMINE

PARAMETER	LSMEAN1	LSMEAN2	LOWCI12	UPPCI12
AUCI	265.09	281.74	90.72	97.46
AUCT	254.85	270.15	90.87	97.80
CMAX	11.37	11.61	93.66	102.28
LAUCI	255.85	273.47	90.35	96.88
LAUCT	245.83	262.00	90.49	97.30
LCMAX	11.16	11.47	93.18	101.67

Table 27. LSMEANS AND 90% CONFIDENCE INTERVALS FOR DESMETHYLSELEGILINE

PARAMETER	LSMEAN1	LSMEAN2	LOWCI12	UPPCI12
AUCI	27.63	28.97	85.59	105.16
AUCT	25.81	27.05	87.70	103.10
CMAX	11.71	12.68	83.64	101.05
LAUCI	25.76	26.45	89.96	105.40
LAUCT	24.19	24.82	91.05	104.30
LCMAX	11.17	11.91	86.65	101.59

11. Non-fasting studies

Table 32. TEST MEAN/REFERENCE MEAN RATIOS (*ANTILOG CONVERSION) FOR SELEGILINE

	MEAN1	SD1	MEAN2	SD2	MEAN3
PARAMETER					
AUCI	471.43	481.42	1041.15	953.23	1452.39
AUCT	402.91	455.84	917.78	937.20	1310.62
CMAX	412.00	290.58	890.47	1128.24	603.00
LAUCI*	372.09	0.61	784.37	0.73	730.15
LAUCT*	297.82	0.71	626.29	0.89	638.75
LCMAX*	341.86	0.62	552.55	0.95	427.72

(CONTINUED)

	SD3	RMEAN12	RMEAN13	RMEAN23
PARAMETER				
AUCI	2293.52	0.45	0.32	0.72
AUCT	2127.32	0.44	0.31	0.70
CMAX	653.12	0.46	0.68	1.48
LAUCI	1.06	0.47	0.51	1.07
LAUCT	1.07	0.48	0.47	0.98
LCMAX	0.76	0.62	0.80	1.29

UNIT: AUC=PG HR/ML CMAX=PG/ML TMAX=HR

Table 36. TEST MEAN/REFERENCE MEAN RATIOS (*ANTILOG CONVERSION) FOR AMPHETAMINE

	MEAN1	SD1	MEAN2	SD2	MEAN3
PARAMETER					
AUCI	94.61	44.44	91.38	33.69	87.82
AUCT	79.86	39.62	81.33	33.14	79.19
CMAX	2.94	0.94	3.00	0.91	3.39
LAUCI*	87.29	0.41	85.13	0.41	82.80
LAUCT*	71.70	0.51	73.42	0.53	74.01
LCMAX*	2.78	0.37	2.84	0.37	3.15

(CONTINUED)

	SD3	RMEAN12	RMEAN13	RMEAN23
PARAMETER				
AUCI	31.54	1.04	1.08	1.04
AUCT	30.72	0.98	1.01	1.03
CMAX	1.46	0.98	0.87	0.89
LAUCI	0.36	1.03	1.05	1.03
LAUCT	0.38	0.98	0.97	0.99
LCMAX	0.38	0.98	0.88	0.90

UNIT: AUC=NG HR/ML CMAX=NG/ML TMAX=HR

Table 40. TEST MEAN/REFERENCE MEAN RATIOS (ANTILOG CONVERSION) FOR METHAMPHETAMINE

	MEAN1	SD1	MEAN2	SD2	MEAN3
PARAMETER					
AUCI	235.45	118.43	237.47	93.31	232.80
AUCT	223.39	106.96	226.68	89.58	222.72
CMAX	10.78	2.88	11.28	2.54	11.06
LAUCI	219.34	0.35	224.80	0.32	222.76
LAUCT	208.66	0.35	214.29	0.33	212.68
LCMAX	10.45	0.25	11.00	0.24	10.85

(CONTINUED)

	SD3	RMEAN12	RMEAN13	RMEAN23
PARAMETER				
AUCI	87.13	0.99	1.01	1.02
AUCT	84.90	0.99	1.00	1.02
CMAX	2.26	0.96	0.97	1.02
LAUCI	0.28	0.98	0.98	1.01
LAUCT	0.29	0.97	0.98	1.01
LCMAX	0.20	0.95	0.96	1.01

UNIT: AUC=NG HR/ML CMAX=NG/ML TMAX=HR

Table 44. TEST MEAN/REFERENCE MEAN RATIOS (*ANTILOG CONVERSION) FOR DESMETHYLSELEGILINE

	MEAN1	SD1	MEAN2	SD2	MEAN3
PARAMETER					
AUCI	36.23	21.66	38.59	20.82	38.38
AUCT	34.44	20.67	36.83	20.14	35.57
CMAX	15.67	8.82	10.17	2.87	9.56
LAUCI*	31.56	0.52	34.20	0.49	34.07
LAUCT*	29.94	0.52	32.52	0.50	31.58
LCMAX*	14.06	0.46	9.76	0.30	9.13

(CONTINUED)

	SD3	RMEAN12	RMEAN13	RMEAN23
PARAMETER				
AUCI	22.81	0.94	0.94	1.01
AUCT	20.87	0.94	0.97	1.04
CMAX	3.09	1.54	1.64	1.06
LAUCI	0.46	0.92	0.93	1.00
LAUCT	0.47	0.92	0.95	1.03
LCMAX	0.30	1.44	1.54	1.07

UNIT: AUC=NG HR/ML CMAX=NG/ML TMAX=HR

JUL 18 1996

Selegiline Hydrochloride Tablets
5 mg Tablet
ANDA #74-565
Reviewer: Moo Park
Filename: 74565A.N95

Endo Labs
Garden City, New York
Submission Date:
November 27, 1995

Review of an Amendment

I. Objective

Review of Endo's response to deficiency letter issued on 10/30/95.

II. Background

Two in vivo bioequivalence studies under fasting and non-fasting conditions were originally submitted on 11/10/94 and an amendment was submitted on 4/20/95. The review of the studies were completed as of 8/31/95 and deficiency letter was issued as of 10/30/95. Summary of PK parameters and statistical analyses was attached as reference.

Endo was informed of the following deficiencies:

1. Concentrations of the internal standard under recovery data for the parent drug and metabolites should be identified.

2. Room temperature stability for metabolites: Storage time is missing.

3. Submitted C_{max} data on a PC diskette are different from the data in hard copy for amphetamine under food conditions.

4. Some of the SAS analysis output were compiled out of order and it causes difficulty reviewing. Care should be taken for future submissions.

5. For future submission of dissolution data, range (high and low) should be reported in addition to the mean, sd, and %CV.

III. Review of Endo's response

1. Concentration of the internal standard under recovery data:

2. Storage time for stability samples at room temperature:

3. PC data diskette: The firm explained that formatting of the data (CMAX of amphetamine) was the reason for the discrepancy.

4. The firm acknowledged deficiencies #4 and 5 concerning the presentation of SAS data and dissolution data. They will correct the deficiencies in the future submissions.

5. Endo's responses to the deficiencies #1-5 are acceptable.

IV. Comments

1. PK parameters for selegiline (parent drug) under fasting conditions: The test/reference ratios (as antilogs) for the log-transformed AUCT, AUCI and CMAX are all within acceptable range of 0.8-1.25.

2. Results of *in vivo* bioequivalence studies under fasting and nonfasting conditions for the parent drug and metabolites met the Agency requirements for bioequivalency as summarized in the earlier review (review date: 8/31/95) and in pp.4-8.

V. Recommendations

1. The *in vivo* bioequivalence studies conducted by Endo Laboratories under fasting and non-fasting conditions comparing its Selegiline Hydrochloride Tablets, 5 mg strength, lot #FE067A, to Somerset Pharmaceuticals' Eldepryl^{R}, 5 mg strength, lot #3Z011D, have been found acceptable by the Division of Bioequivalence. The studies demonstrated that Endo's Selegiline Hydrochloride Tablets, 5 mg strength, is bioequivalent to the reference product, Somerset Pharmaceuticals' Eldepryl^{R}, 5 mg strength.

2. The dissolution testing conducted by Endo Laboratories on its Selegiline Hydrochloride Tablets, 5 mg strength, Lot # FE067A, is acceptable.

3. The dissolution testing should be conducted on 12 units of the product in 500 mL of water at 37°C using USP 23 apparatus 2 (paddle) at 50 rpm. The test product should meet the following specifications:

   Not less than of the labeled amount of the drug in the dosage form is dissolved in 30 minutes.

4. From the bioequivalence point of view, the firm has met the *in vivo* and *in vitro* bioequivalence requirements and the submission is approvable.

The firm should be informed of the recommendations.

Moo Park, Ph.D.
Review Branch III

SUMMARY OF ANDA #74-565:

The data tables used in the summary were copied from the text of the original review (review date:8/31/96) and the table No's were left unchanged for easier referencing.

I. Fasting studies

Table 11. TEST MEAN/REFERENCE MEAN RATIOS (*ANTILOG CONVERSION) For Selegiline

	MEAN1	SD1	MEAN2	SD2	RMEAN12
PARAMETER					
AUCI	749.89	1418.16	532.78	580.68	1.41
AUCT	618.41	1280.54	445.63	541.40	1.39
CMAX	684.97	1101.17	644.69	811.31	1.06
LAUCI*	346.37	1.07	356.64	0.87	0.97
LAUCT*	262.19	1.11	272.01	0.97	0.96
LCMAX*	358.01	1.01	398.57	0.96	0.90

UNIT: AUC=PG HR/ML CMAX=PG/ML TMAX=HR

Table 12. LSMEANS AND 90% CONFIDENCE INTERVALS FOR SELEGILINE

	LSMEAN1	LSMEAN2	LOWCI12	UPPCI12
PARAMETER				
AUCI	695.42	407.07	70.94	270.73
AUCT	632.72	444.25	75.17	209.67
CMAX	698.70	645.92	78.60	137.75
LAUCI	310.10	322.75	84.28	109.53
LAUCT	266.59	270.30	85.42	113.87
LCMAX	363.17	396.66	78.09	107.35

LSMEAN1=LSMEAN FOR THE TEST PRODUCT
LSMEAN2=LSMEAN FOR THE REFERENCE PRODUCT

Table 17. LSMEANS AND 90% CONFIDENCE INTERVALS FOR AMPHETAMINE

	LSMEAN1	LSMEAN2	LOWCI12	UPPCI12
PARAMETER				
AUCI	91.39	96.01	91.25	99.12
AUCT	77.61	82.30	89.06	99.54
CMAX	2.89	2.92	93.26	104.24
LAUCI	88.76	93.72	90.95	98.63
LAUCT	74.65	79.73	88.08	99.54
LCMAX	2.81	2.88	92.76	102.98

Table 22. LSMEANS AND 90% CONFIDENCE INTERVALS FOR METHAMPHETAMINE

	LSMEAN1	LSMEAN2	LOWCI12	UPPCI12
PARAMETER				
AUCI	265.09	281.74	90.72	97.46
AUCT	254.85	270.15	90.87	97.80
CMAX	11.37	11.61	93.66	102.28
LAUCI	255.85	273.47	90.35	96.88
LAUCT	245.83	262.00	90.49	97.30
LCMAX	11.16	11.47	93.18	101.67

Table 27. LSMEANS AND 90% CONFIDENCE INTERVALS FOR DESMETHYLSELEGILINE

	LSMEAN1	LSMEAN2	LOWCI12	UPPCI12
PARAMETER				
AUCI	27.63	28.97	85.59	105.16
AUCT	25.81	27.05	87.70	103.10
CMAX	11.71	12.68	83.64	101.05
LAUCI	25.76	26.45	89.96	105.40
LAUCT	24.19	24.82	91.05	104.30
LCMAX	11.17	11.91	86.65	101.59

II. Non-fasting studies

Table 32. TEST MEAN/REFERENCE MEAN RATIOS (*ANTILOG CONVERSION) FOR SELEGILINE

	MEAN1	SD1	MEAN2	SD2	MEAN3
PARAMETER					
AUCI	471.43	481.42	1041.15	953.23	1452.39
AUCT	402.91	455.84	917.78	937.20	1310.62
CMAX	412.00	290.58	890.47	1128.24	603.00
LAUCI*	372.09	0.61	784.37	0.73	730.15
LAUCT*	297.82	0.71	626.29	0.89	638.75
LCMAX*	341.86	0.62	552.55	0.95	427.72

(CONTINUED)

	SD3	RMEAN12	RMEAN13	RMEAN23
PARAMETER				
AUCI	2293.52	0.45	0.32	0.72
AUCT	2127.32	0.44	0.31	0.70
CMAX	653.12	0.46	0.68	1.48
LAUCI	1.06	0.47	0.51	1.07
LAUCT	1.07	0.48	0.47	0.98
LCMAX	0.76	0.62	0.80	1.29

UNIT: AUC=PG HR/ML CMAX=PG/ML TMAX=HR

Table 36. TEST MEAN/REFERENCE MEAN RATIOS (*ANTILOG CONVERSION) FOR AMPHETAMINE

	MEAN1	SD1	MEAN2	SD2	MEAN3
PARAMETER					
AUCI	94.61	44.44	91.38	33.69	87.82
AUCT	79.86	39.62	81.33	33.14	79.19
CMAX	2.94	0.94	3.00	0.91	3.39
LAUCI*	87.29	0.41	85.13	0.41	82.80
LAUCT*	71.70	0.51	73.42	0.53	74.01
LCMAX*	2.78	0.37	2.84	0.37	3.15

(CONTINUED)

	SD3	RMEAN12	RMEAN13	RMEAN23
PARAMETER				
AUCI	31.54	1.04	1.08	1.04
AUCT	30.72	0.98	1.01	1.03
CMAX	1.46	0.98	0.87	0.89
LAUCI	0.36	1.03	1.05	1.03
LAUCT	0.38	0.98	0.97	0.99
LCMAX	0.38	0.98	0.88	0.90

UNIT: AUC=NG HR/ML CMAX=NG/ML TMAX=HR

Table 40. TEST MEAN/REFERENCE MEAN RATIOS (ANTILOG CONVERSION) FOR METHAMPHETAMINE

	MEAN1	SD1	MEAN2	SD2	MEAN3
PARAMETER					
AUCI	235.45	118.43	237.47	93.31	232.80
AUCT	223.39	106.96	226.68	89.58	222.72
CMAX	10.78	2.88	11.28	2.54	11.06
LAUCI	219.34	0.35	224.80	0.32	222.76
LAUCT	208.66	0.35	214.29	0.33	212.68
LCMAX	10.45	0.25	11.00	0.24	10.85

(CONTINUED)

	SD3	RMEAN12	RMEAN13	RMEAN23
PARAMETER				
AUCI	87.13	0.99	1.01	1.02
AUCT	84.90	0.99	1.00	1.02
CMAX	2.26	0.96	0.97	1.02
LAUCI	0.28	0.98	0.98	1.01
LAUCT	0.29	0.97	0.98	1.01
LCMAX	0.20	0.95	0.96	1.01

UNIT: AUC=NG HR/ML CMAX=NG/ML TMAX=HR

Table 44. TEST MEAN/REFERENCE MEAN RATIOS (*ANTILOG CONVERSION) FOR DESMETHYLSELEGILINE

	MEAN1	SD1	MEAN2	SD2	MEAN3
PARAMETER					
AUCI	36.23	21.66	38.59	20.82	38.38
AUCT	34.44	20.67	36.83	20.14	35.57
CMAX	15.67	8.82	10.17	2.87	9.56
LAUCI*	31.56	0.52	34.20	0.49	34.07
LAUCT*	29.94	0.52	32.52	0.50	31.58
LCMAX*	14.06	0.46	9.76	0.30	9.13

(CONTINUED)

	SD3	RMEAN12	RMEAN13	RMEAN23
PARAMETER				
AUCI	22.81	0.94	0.94	1.01
AUCT	20.87	0.94	0.97	1.04
CMAX	3.09	1.54	1.64	1.06
LAUCI	0.46	0.92	0.93	1.00
LAUCT	0.47	0.92	0.95	1.03
LCMAX	0.30	1.44	1.54	1.07

UNIT: AUC=NG HR/ML CMAX=NG/ML TMAX=HR

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1. CHEMIST'S REVIEW NO.3

2. ANDA # 74-565

3. NAME AND ADDRESS OF APPLICANT
Endo Laboratories, L.L.C.
Attention: Ms. Carol Patterson
1000 Stewart Avenue
Garden City, NY 11530

4. BASIS FOR SUBMISSION:

The applicant includes patent and exclusivity information on page 2. The firm claims that there are no patents for the innovator's product. The drug is covered by an Orphan Drug Exclusivity which will expire on June 5, 1996.

5. SUPPLEMENT(s)
N/A

6. PROPRIETARY NAME
Eldepryl Tablets

7. NONPROPRIETARY NAME
Selegiline Hydrochloride, USP

8. SUPPLEMENT(s) PROVIDE(s) FOR:
N/A

9. AMENDMENTS AND OTHER DATES:

Original Submission	November 14, 1994
Acknowledgement letter	February 2, 1995
New Correspondence	January 5, 1995
FDA deficiency letter	April 28, 1995
Amendment to CMC	July 7, 1995
FDA Deficiency Letter	February 12, 1996
Amendment to CMC	April 4, 1996
Amendment to CMC	June 18, 1996

10. PHARMACOLOGICAL CATEGORY
Antiparkinsonian

11. Rx or OTC
Rx

12. RELATED IND/NDA/DMF(s)

Comment:

The firm was requested to insure that all pertinent DMF references are listed on the 356h form.

The applicant responded that all of the references are listed. They noted that the DMF reference #1016 has been withdrawn. **Satisfactory**

13. DOSAGE FORM
Tablet

14. POTENCY
5 mg

15. CHEMICAL NAME AND STRUCTURE
(-)-R-N, - alpha-dimethy-N-2-propynl phenethylamine hydrochloride

16. RECORDS AND REPORTS
N/A

17. COMMENTS
All chemistry deficiencies have been resolved.

18. CONCLUSIONS AND RECOMMENDATIONS
The application is now approvable.

19. REVIEWER:
Karen A. Bernard, Ph.D.

DATE COMPLETED:
May 9, 1996

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER 074565

BIOEQUIVALENCE REVIEW(S)

JUL 24 1996

Selegiline Hydrochloride Tablets
5 mg Tablet
ANDA #74-565
Reviewer: Moo Park
Filename: 74565AAD.N95

Endo Labs
Garden City, New York
Submission Date:
November 27, 1995

Review of an Amendment (Addendum)

I. Objective and Background

New dissolution specifications were adopted in USP 23, Supplement 4. Therefore, the firm is recommended to use the USP dissolution specifications in place of Pharmaceutical Forum method (March-April, 1994). Endo previously submitted dissolution data by the PF and USP (It was FDA method then.) and data met both specifications.

PF method:

Medium: water, 500 mL
Temperature: 37°C
Apparatus: 2(paddle)
Rotation: 50 rpm
Specifications: NLT (Q) in 30 min.

USP method:

Medium: water, 500mL
Temperature: 37°C
Apparatus: 1(basket)
Rotation: 50 rpm
Specifications: NLT (Q) in 20 min.

II. Recommendation

The following paragraph replaces the paragraph regarding dissolution in the recommendation of the review of amendment dated 11/27/95:

3. The dissolution testing should be conducted on 12 units of the product in 500 mL of water at 37°C using USP 23 apparatus 1 (basket) at 50 rpm. The test product should meet the following specifications:

   Not less than f the labeled amount of the drug in the dosage form is dissolved in 20 minutes.

Moo Park, PH.D.
Review Branch III
The Division of Bioequivalence

RD INITIALED RMHATRE
FT INITIALED RMHATRE Ramanbhai M. Mhatre 7/24/96

Selegiline Hydrochloride Tablets
5 mg Tablet
ANDA #74-565
Reviewer: Moo Park
Filename: 74565SD.N94

Endo Labs
Garden City, New York
Submission Date:
November 10, 1994
April 20, 1995

Review of Two *IN VIVO* Bioequivalence Studies and Dissolution Data

SUMMARY OF ANDA #74-565:

The data tables used in the summary were copied from the text of this review and the table No's were left unchanged for easier referencing.

I. Fasting studies

Table 12. LSMEANS AND 90% CONFIDENCE INTERVALS FOR SELEGILINE

	LSMEAN1	LSMEAN2	LOWCI12	UPPCI12
PARAMETER				
AUCI	695.42	407.07	70.94	270.73
AUCT	632.72	444.25	75.17	209.67
CMAX	698.70	645.92	78.60	137.75
LAUCI	310.10	322.75	84.28	109.53
LAUCT	266.59	270.30	85.42	113.87
LCMAX	363.17	396.66	78.09	107.35

LSMEAN1=LSMEAN FOR THE TEST PRODUCT
LSMEAN2=LSMEAN FOR THE REFERENCE PRODUCT

Table 17. LSMEANS AND 90% CONFIDENCE INTERVALS FOR AMPHETAMINE

	LSMEAN1	LSMEAN2	LOWCI12	UPPCI12
PARAMETER				
AUCI	91.39	96.01	91.25	99.12
AUCT	77.61	82.30	89.06	99.54
CMAX	2.89	2.92	93.26	104.24
LAUCI	88.76	93.72	90.95	98.63
LAUCT	74.65	79.73	88.08	99.54
LCMAX	2.81	2.88	92.76	102.98

Table 22. LSMEANS AND 90% CONFIDENCE INTERVALS FOR METHAMPHETAMINE

	LSMEAN1	LSMEAN2	LOWCI12	UPPCI12
PARAMETER				
AUCI	265.09	281.74	90.72	97.46
AUCT	254.85	270.15	90.87	97.80
CMAX	11.37	11.61	93.66	102.28
LAUCI	255.85	273.47	90.35	96.88
LAUCT	245.83	262.00	90.49	97.30
LCMAX	11.16	11.47	93.18	101.67

Table 27. LSMEANS AND 90% CONFIDENCE INTERVALS FOR DESMETHYLSELEGILINE

	LSMEAN1	LSMEAN2	LOWCI12	UPPCI12
PARAMETER				
AUCI	27.63	28.97	85.59	105.16
AUCT	25.81	27.05	87.70	103.10
CMAX	11.71	12.68	83.64	101.05
LAUCI	25.76	26.45	89.96	105.40
LAUCT	24.19	24.82	91.05	104.30
LCMAX	11.17	11.91	86.65	101.59

II. Non-fasting studies

Table 32. TEST MEAN/REFERENCE MEAN RATIOS (*ANTILOG CONVERSION) FOR SELEGILINE

	MEAN1	SD1	MEAN2	SD2	MEAN3
PARAMETER					
AUCI	471.43	481.42	1041.15	953.23	1452.39
AUCT	402.91	455.84	917.78	937.20	1310.62
CMAX	412.00	290.58	890.47	1128.24	603.00
LAUCI*	372.09	0.61	784.37	0.73	730.15
LAUCT*	297.82	0.71	626.29	0.89	638.75
LCMAX*	341.86	0.62	552.55	0.95	427.72

(CONTINUED)

	SD3	RMEAN12	RMEAN13	RMEAN23
PARAMETER				
AUCI	2293.52	0.45	0.32	0.72
AUCT	2127.32	0.44	0.31	0.70
CMAX	653.12	0.46	0.68	1.48
LAUCI	1.06	0.47	0.51	1.07
LAUCT	1.07	0.48	0.47	0.98
LCMAX	0.76	0.62	0.80	1.29

UNIT: AUC=PG HR/ML CMAX=PG/ML TMAX=HR

Table 36. TEST MEAN/REFERENCE MEAN RATIOS (*ANTILOG CONVERSION) FOR AMPHETAMINE

	MEAN1	SD1	MEAN2	SD2	MEAN3
PARAMETER					
AUCI	94.61	44.44	91.38	33.69	87.82
AUCT	79.86	39.62	81.33	33.14	79.19
CMAX	2.94	0.94	3.00	0.91	3.39
LAUCI*	87.29	0.41	85.13	0.41	82.80
LAUCT*	71.70	0.51	73.42	0.53	74.01
LCMAX*	2.78	0.37	2.84	0.37	3.15

(CONTINUED)

	SD3	RMEAN12	RMEAN13	RMEAN23
PARAMETER				
AUCI	31.54	1.04	1.08	1.04
AUCT	30.72	0.98	1.01	1.03
CMAX	1.46	0.98	0.87	0.89
LAUCI	0.36	1.03	1.05	1.03
LAUCT	0.38	0.98	0.97	0.99
LCMAX	0.38	0.98	0.88	0.90

UNIT: AUC=NG HR/ML CMAX=NG/ML TMAX=HR

Table 40. TEST MEAN/REFERENCE MEAN RATIOS (ANTILOG CONVERSION) FOR METHAMPHETAMINE

PARAMETER	MEAN1	SD1	MEAN2	SD2	MEAN3
AUCI	235.45	118.43	237.47	93.31	232.80
AUCT	223.39	106.96	226.68	89.58	222.72
CMAX	10.78	2.88	11.28	2.54	11.06
LAUCI	219.34	0.35	224.80	0.32	222.76
LAUCT	208.66	0.35	214.29	0.33	212.68
LCMAX	10.45	0.25	11.00	0.24	10.85

(CONTINUED)

PARAMETER	SD3	RMEAN12	RMEAN13	RMEAN23
AUCI	87.13	0.99	1.01	1.02
AUCT	84.90	0.99	1.00	1.02
CMAX	2.26	0.96	0.97	1.02
LAUCI	0.28	0.98	0.98	1.01
LAUCT	0.29	0.97	0.98	1.01
LCMAX	0.20	0.95	0.96	1.01

UNIT: AUC=NG HR/ML CMAX=NG/ML TMAX=HR

Table 44. TEST MEAN/REFERENCE MEAN RATIOS (*ANTILOG CONVERSION) FOR DESMETHYLSELEGILINE

PARAMETER	MEAN1	SD1	MEAN2	SD2	MEAN3
AUCI	36.23	21.66	38.59	20.82	38.38
AUCT	34.44	20.67	36.83	20.14	35.57
CMAX	15.67	8.82	10.17	2.87	9.56
LAUCI*	31.56	0.52	34.20	0.49	34.07
LAUCT*	29.94	0.52	32.52	0.50	31.58
LCMAX*	14.06	0.46	9.76	0.30	9.13

(CONTINUED)

	SD3	RMEAN12	RMEAN13	RMEAN23
PARAMETER				
AUCI	22.81	0.94	0.94	1.01
AUCT	20.87	0.94	0.97	1.04
CMAX	3.09	1.54	1.64	1.06
LAUCI	0.46	0.92	0.93	1.00
LAUCT	0.47	0.92	0.95	1.03
LCMAX	0.30	1.44	1.54	1.07

UNIT: AUC=NG HR/ML CMAX=NG/ML TMAX=HR

I. Objective

Review of Endo's *in vivo* bioequivalence studies under fasting and food conditions comparing its Selegiline Hydrochloride Tablets, 5 mg strength, to Somerset's Eldepryl[R] Tablets, 5 mg strength, and comparative dissolution testing data.

The sponsor submitted the following information for review:

(1). In vivo bioequivalence study under fasting conditions: The parent drug, selegiline, and its three metabolites were assayed and analyzed statistically.

(2). In vivo bioequivalence study under non-fasting conditions: The parent drug, selegiline, and its three metabolites were assayed and analyzed statistically.

(3). Analytical method validation data

(4). Dissolution data

II. Background

Selegiline hydrochloride is a levorotatory acetylenic derivative of phenethylamine. It is commonly referred to in the clinical and pharmacological literature as L-deprenyl. The chemical name is: (R)-(-)-N,2-dimethyl-N-2-propynylphenethylamine hydrochloride. It is a white to near white crystalline powder, freely soluble in water, chloroform, and methanol, and has a molecular weight of 223.75.

The mechanisms accounting for selegiline's beneficial adjunctive action in the treatment of Parkinson's disease are not fully understood. Inhibition of monoamine oxidase, type B, activity is generally considered to be of primary importance; in addition, there is evidence that selegiline may act through other mechanisms to increase dopaminergic activity. Selegiline is best known as an irreversible inhibitor of monoamine oxidase (MAO). Because selegiline has greater affinity for type B than for Type A active sites, it can serve as a selective inhibitor of MAO type B if it is administered at the recommended dose. In humans, intestinal MAO is predominantly type A, while most of that in brain is type B. In CNS neurons, MAO plays an important role in the catabolism of catecholamines.

Only preliminary information about the details of the pharmacokinetics of selegiline and its metabolites is available. Following the oral administration of a single dose of 10 mg of selegiline hydrochloride to 12 healthy subjects, serum levels of intact selegiline were below the limit of detection (less than 10

ng/ml). Three metabolites, N-desmethyl deprenyl, the major metabolite (mean half-life 2.0 hours), amphetamine (mean half-life 17.7 hours), and methamphetamine (mean half-life 20.5 hours), were found in serum and urine. Over a period of 48 hours, 45% of the dose administered appeared in the urine as these 3 metabolites. In an extension of this study intended to examine the effects of steady state conditions, the same subjects were given a 10 mg dose of selegiline hydrochloride for seven consecutive days. Under these conditions, the mean trough serum levels for amphetamine were 3.5 ng/ml and 8.0 ng/ml for methamphetamine; trough levels of N-desmethyldeprenyl were below the levels of detection.

Selegiline is intended for administration in Parkinsonian patients who demonstrate a deteriorating response to levodopa/carbidopa treatment. The recommended regimen for the administration of selegiline is 10 mg per day administered as divided doses of 5 mg each taken at breakfast and lunch. There is no evidence that additional benefit will be obtained from the administration of higher doses.

III. Bio-study Details

The firm conducted a total of two *in vivo* bioequivalence studies under fasting and nonfasting conditions. In each study, plasma levels and pharmacokinetic parameters for the parent drug and its three metabolites were determined and used for statistical analyses. Details of the fasting and nonfasting studies are shown below:

A. Study under Fasting Conditions

1. Protocol #003-01

2. Sponsor: The DuPont Merck Pharmaceutical Company
Barley Mill Plaza P27/1278
PO Box 80027
Wilmington, DE 19880-0027

3. Study sites:
Clinical study:

Analytical:

4. Investigators:
Principal investigator:

Study monitors:

Clinical Pharmacology

5. Clinical study dates: March 4-23, 1994

   Assay dates: March 30-May 5, 1994

6. Study design: Single-center, open-label, randomized, two-way crossover study.

7. Dosing and product information:
   (a) Test product: 5 mg Selegiline HCl Tablets (The DuPont Merck Pharmaceutical Company)
   Route of Administration: Oral
   Dosage Regimen: Single dose, 10 mg (2 x 5 mg)
   Lot Number: FE067A
   Assay: 100.8%
   Content uniformity: 100.6%(1.8%CV)
   Batch size:

   (b) Reference product: 5 mg Selegiline (Eldepryl^{R} tablets, Somerset Pharmaceuticals, Inc.)

   Route of Administration: Oral
   Dosage Regimen: Single dose, 10 mg (2 x 5 mg)
   Lot Number: 3Z011D
   Assay: 101.7%
   Content uniformity: Not available.
   Expiration date: 10/94

8. Subjects: Forty subjects were simultaneously enrolled in this study in order to ensure that 36 subjects completed all treatment periods.

   Subjects meeting the selection criteria underwent screening evaluations within the 14 days prior to receiving the study medication. A urine drug screen and HIV, HBsAg, and HAV antibody screens were performed. Positive results in the drug screen, hepatitis screen, or HIV test resulted in exclusion from the study. A retest following a positive result was not permitted.

   Screening evaluations, consisting of a medical history, medication history, physical examination (including vital signs), and a clinical laboratory evaluation (including serum chemistry, hematology, and urinalysis) were also performed.

9. Food and fluid intake: Each subject received a single oral dose of 10 mg Selegiline,

administered as two 5 mg tablets (test or reference), on the mornings of Study Days 1 and 15 under fasting conditions. Each dose of medication was to be taken with 240 mL of water following a 10-hour (minimum) fast. All subjects fasted for 4 hours following each dose. Water was allowed ad libitum except for 1 hour prior to and 1 hour after drug administration.

10. Washout period: Two weeks

11. Blood samples: Samples were collected for selegiline analysis into Vacutainer^{R} tubes containing sodium heparin immediately before (0 hour) and at the following times postdose on Study Days 1 and 15: 15, 30, 45 minutes, and at 1, 1.25, 1.5, 2, 2.5, 3, 4, 6, and 8 hours for selegiline. Samples for metabolite analysis were collected immediately before (0 hour) and at 15, 30, and 45 minutes, and at 1, 1.25, 1.5, 2, 3, 4, 6, 8, 12, 16, 24, 48, 72, and 96 hours following drug administration on Study Days 1 and 15.

    The samples were centrifuged within 20 minutes of collection, and the plasma was transferred with a disposable pipette to a polypropylene tube bearing identifying labels showing the study number, the subject number, the time and date of the sample, and whether the sample was for selegiline or metabolite analysis. The samples were placed in a freezer within 40 minutes of collection and stored at 70°C until shipped for analysis.

12. Urine samples: No samples collected.

13. Subject monitoring: Subjects were required to report to the study site during the evening prior to the first dose of study medication and remained in confinement for approximately 36 hours. Blood samples were obtained through the 96 hours after dosing. Subjects were released from the study site following completion of the 24-hour postdose sample collection and were required to return for the scheduled postdose sample collection at 48 (Study Day 3), 72 (Study Day 4) and 96 hours (Study Day 5) on an outpatient basis.

On Study Day 14, subjects returned to the study site and remained in confinement for approximately 36 hours in order to receive the second dose of study medication. For the 48(Study Day 17), 72-(Study Day 18), and 96-hour (Study Day 19) sample collection, subjects returned on an outpatient basis. On Study Day 19, end-of-study evaluations were completed. Subjects were continually monitored for adverse events throughout confinement. At the beginning of the subsequent treatment period, the subjects were questioned concerning unusual symptoms which may have occurred after the previous administration of study drug. Symptoms that may have been related to the study drug were evaluated by the investigator, or a medically qualified designee, before the next dose was administered .

14. Statistical analysis: SAS-GLM procedures were used on AUC_t, AUC_{inf}, C_{max}, T_{max}, K_{el}, $t_{1/2}$ and plasma levels at each sampling points. The 90% confidence intervals (CI) were calculated for AUC_t, AUC_{inf} and C_{max}.

B. Study under Nonfasting Conditions

1. Protocol #004-01

2. Sponsor: The DuPont Merck Pharmaceutical Company
Barley Mill Plaza P27/1278
PO Box 80027
Wilmington, DE 19880-0027

3. Study sites:
Clinical study:

Analytical:

4. Investigators:
Principal investigator:

Study monitors:

5. Clinical study dates: February 12-March 17, 1994

   Assay dates: March 24-May 26, 1994

6. Study design: Single-center, open-label, randomized, three-way crossover study.

7. Dosing and product information:
   (a) Test product: 5 mg Selegiline HCl Tablets (The DuPont Merck Pharmaceutical Company) under fasting conditions.

   Route of Administration: Oral
   Dosage Regimen: Single dose, 10 mg (2 x 5 mg)
   Lot Number: FE067A
   Assay: 100.8%
   Content uniformity:100.6%(1.8% CV)
   Batch size

   (b) Test product: 5 mg Selegiline tablets (The DuPont Merck Pharmaceutical Company) under food conditions.

   Route of Administration: Oral
   Dosage Regimen: Single dose, 10 mg (2 x 5 mg)
   Lot Number: FE067A

   (c) Reference product: 5 mg selegiline (Eldepryl^{R} tablets, Somerset Pharmaceuticals, Inc.) under food conditions.

   Route of Administration: Oral
   Dosage Regimen: Single dose, 10 mg (2 x 5 mg)
   Lot Number: 3Z011D
   Assay: 101.7%
   Content uniformity: N/A
   Expiration date: 10/94

8. Subjects: Twenty subjects were simultaneously enrolled in this study in order to ensure that 18 subjects completed all treatment periods.

   Subjects meeting the selection criteria underwent screening evaluations within the 14 days prior to receiving the study medication. A urine drug screen and HIV, HBsAg, and HAV antibody screens were performed. Positive results in the drug screen, hepatitis screen, or HIV test resulted in exclusion from the study. A retest following a positive

result was not permitted.

Screening evaluations, consisting of a medical history, medication history, physical examination (including vital signs), and a clinical laboratory evaluation (including serum chemistry, hematology, and urinalysis) were also performed.

9. Food and fluid intake: Subjects assigned to Treatment A (fasting condition; selegiline 2 x 5 mg; The DuPont Merck Pharmaceutical Company) fasted overnight for 10 hours and then received a 10 mg dose. Subjects assigned to Treatment B (non-fasting condition; selegiline 2 x 5 mg; The DuPont Merck Pharmaceutical Company) or Treatment C (non-fasting condition; Eldepryl® 2 x 5 mg) fasted overnight for 10 hours, ate a standard breakfast 20 minutes before dosing, and then received a 10 mg dose. The breakfast consisted of one buttered English muffin, one fried egg, one slice of American cheese, one rasher of Canadian bacon, hashed brown potatoes, 180 mL orange juice, and 240 mL whole milk. For all subjects, each dose of medication was taken with 240 mL of water within 5 minutes of completing the meal. All subjects were required to fast and to remain in an upright position for the 4 hours following dose administration. Water was allowed ad libitum except for the 1 hour prior to and the 1 hour following dose administration.

10. Washout period: Two weeks

11. Blood samples: Venous blood samples, collected into 10-mL Vacutainer® tubes containing sodium heparin to determine selegiline plasma concentrations, were obtained immediately before (0 hour) and at 15, 30, 45 minutes, and at 1, 1.25, 1.5, 2, 2.5, 3, 4, 6, and 8 hours following drug administration on Study Days 1, 15, and 29.

Venous blood samples, collected into 7-mL Vacutainer® tubes containing sodium heparin to determine metabolite desmethylselegiline,

amphetamine, and methamphetamine) concentrations, were obtained immediately before (0 hour) and at 15, 30, 45 minutes, and at 1, 1.25, 1.5, 2, 3, 4, 6, 8, 12, 16, 24, 48, 72, and 96 hours following drug administration on Study Days 1, 15, and 29.

The samples were centrifuged within 20 minutes of collection, and the plasma was transferred with a disposable pipette to a polypropylene tube bearing identifying labels showing the study number, the subject number, the time and date of sample, and whether the sample was for selegiline or metabolite analysis. The samples were placed in a freezer within 40 minutes of collection and stored at -70°C until shipped for analysis.

12. Urine samples: No samples were collected.

13. Subject monitoring: Subjects were required to report to the study site during the evening prior to the first dose of study medication and remained in confinement for approximately 36 hours. Blood samples were obtained through the 96 hours after dosing. Subjects were released from the study site following completion of the 24-hour postdose sample collection and were required to return for the scheduled postdose sample collection on Study Days 3, 4, and 5, on an outpatient basis.

On Study Day 14, subjects returned to the study site and remained in confinement for approximately 36 hours to receive the second dose of study medication. For the 48 (Study Day 17), 72 (Study Day 18), and 96 (Study Day 19) hour sample collection, subjects returned to the study site on an outpatient basis. On Study Day 28, subjects returned to the study site and remained in confinement for approximately 36 hours to receive the third dose of study medication. For the 48 (Study Day 31), 72 (Study Day 32), and 96 (Study Day 33) hour sample collection, subjects returned to the study site on an outpatient basis. On Study Day 33, end-of-study evaluations were completed .

Subjects were continually monitored for

adverse events throughout confinement. At the beginning of the subsequent treatment periods, the subjects were questioned concerning unusual symptoms which may have occurred after the previous administration of study drug. Symptoms that may have been related to the study drug were evaluated by the investigator, or a medically qualified designee, before the next dose was administered .

14. Statistical analysis: SAS-GLM procedures were used on AUC_t, AUC_{inf}, C_{max}, T_{max}, K_{el}, $t_{1/2}$ and plasma levels at each sampling points. The Test/Reference mean ratios were calculated for the pharmacokinetic parameters.

IV. Validation of Assay Method for Plasma Samples

Table 1. Assay of Selegiline in Quality Control Samples

Theoretical Conc pg/mL	N	Found Mean pg/mL	Precision Overall %CV	Accuracy %Difference
Fasting Study				
Food Study				

Table 2. Precision and Accuracy of Selegiline Assay
Method Validation Report

Theoretical Conc	N	Found Mean	Precision Inter- Intra-Assay	Accuracy
pg/mL		pg/mL	%CV	%Difference

5. Recovery: The recovery data in the method validation report have missing concentrations as shown in Table 3.

Table 3. Absolute Recovery of Selegiline
Method Validation Report

Concentration, pg/mL	N	%Recovery	%CV

(Internal Standard)

6.

Table 5. Assay of Three Metabolites in Quality Control Samples

Theoretical Conc ng/mL	N	Found Mean ng/mL	Precision Overall %CV	Accuracy %Difference
Amphetamine:				
Fasting Study				
Food Study				
Methamphetamine:				
Fasting Study				
Food Study				

Desmethylselegiline:

Fasting Study

Food Study

Table 6. Precision and Accuracy of Metabolites Assay Method Validation Report

Theoretical Conc	N	Found Mean	Precision Inter- Intra-Assay	Accuracy
ng/mL		ng/mL	%CV	%Difference

V. In Vivo Results with Statistical Analysis

A. Study under Fasting Conditions

A total of 40 healthy male subjects participated in the study and Subject #20 was discontinued from the study before starting the 2nd period because of a positive alcohol screening. Thirty-nine subjects completed the fasting study.

There were no clinically significant abnormal laboratory values or significant changes in the vital signs during the course of the study.

A total of 11 adverse events (paresthesia, dizziness, syncope, headache, rash, etc.) were reported by 9 subjects. All events (8 events for the test product and 3 events for the reference product) were not serious and no subjects were withdrawn from the study because of the adverse events.

Data for the plasma levels, pharmacokinetic parameters and the statistical analyses were summarized for each of the parent drug and its three metabolites.

1. Selegiline

The plasma levels of selegiline were so low with several subjects that the data from those subjects were removed from the statistical analyses by the reviewer. There were several subjects who had only three or fewer than three non-zero plasma selegiline levels out of 13 sampling time points for the plasma selegiline-time profile. Table 9 summarizes the number of subjects showing non-zero plasma selegiline levels. A total of 29 subjects, who showed no less than four non-zero plasma selegiline levels in the plasma selegiline-time profile, were used to analyze the plasma levels and pharmacokinetic parameters of selegiline.

Table 9. Subjects Showing Non-zero Selegiline Levels
Fasting Study

No. of Non-zero Levels	Subject # Test Product	Ref Product	Total
0	40	36,40	2
1	-	-	0
2	4,7,36	8,17,30	6
3	5,6,8,21	5,7,21	5
4 or more	(31 subjects)	(31 subjects)	34*

*Only 29 subjects met the criterion for both the test and reference products.

(a). Mean plasma levels

For 10 subjects the plasma levels were so low that meaningful profiles could not be obtained and the inter-subject variability is extremely high. Table 10 shows that the inter-subject variability at 0.5 hours was 205% CV and 173% CV for the test and reference products, respectively. The peaks of the mean plasma levels, 448 pg/mL for the test product and 452 pg/mL for the reference product, were observed at 0.5 hours. Table 10 also shows that the variability is higher for the test product than for the reference product over all the sampling period. Figure 1 shows the plasma level-time profiles.

Table 10. MEAN PLASMA SELEGILINE LEVELS FOR TEST AND REFERENCE PRODUCTS (N=29, Unit=pg/mL)

	MEAN1	SD1	MEAN2	SD2	RMEAN12
TIME HR					
0	0.00	0.00	0.00	0.00	.
0.25	29.89	96.27	37.07	74.17	0.81
0.5	448.37	919.76	451.51	779.21	0.99
0.75	423.66	576.16	386.35	376.07	1.10
1	281.57	376.88	322.55	454.10	0.87
1.25	276.15	729.89	181.34	249.69	1.52
1.5	228.39	701.53	144.80	276.19	1.58
2	137.98	428.01	53.62	100.91	2.57
2.5	58.48	182.35	26.38	61.98	2.22
3	49.05	138.92	10.95	24.99	4.48
4	18.56	66.41	5.44	21.42	3.41
6	7.34	32.71	2.20	11.85	3.34
8	5.21	20.64	0.00	0.00	.

MEAN1=TEST PRODUCT
MEAN2=REFERENCE PRODUCT
SD1=STANDARD DEVIATION FOR THE TEST PRODUCT
SD2=STANDARD DEVIATION FOR THE REFERENCE PRODUCT
RMEAN12=TEST MEAN/REFERENCE MEAN RATIO

(b). Pharmacokinetic parameters

The variability of the pharmacokinetic parameters was found to be very high reflecting the variability of the plasma levels. The AUC's showed a CV of approximately 200% and 100% for the test and reference products, respectively. The Cmax also showed a similar magnitude of variability. See Table 11.

The test/reference ratios for the AUC_t, AUC_i and C_{max} were 1.39, 1.41 and 1.06, respectively, for the non-transformed data and 0.96, 0.97 and 0.90 for the log-transformed data.

As shown in Table 12, the 90% confidence intervals (CI) for the log-transformed AUC_t, AUC_i and C_{max} were 85-114, 84-110 and 78-107. The sponsor, however, reported a 90% CI of 82-115 for the log-transformed C_{max} by analyzing 38 subjects.

The 90% CI for the log-transformed C_{max} does not meet the Division's requirement of 80-125%.

Table 11. TEST MEAN/REFERENCE MEAN RATIOS (*ANTILOG CONVERSION)

	MEAN1	SD1	MEAN2	SD2	RMEAN12
PARAMETER					
AUCI	749.89	1418.16	532.78	580.68	1.41
AUCT	618.41	1280.54	445.63	541.40	1.39
CMAX	684.97	1101.17	644.69	811.31	1.06
LAUCI*	346.37	1.07	356.64	0.87	0.97
LAUCT*	262.19	1.11	272.01	0.97	0.96
LCMAX*	358.01	1.01	398.57	0.96	0.90

UNIT: AUC=PG HR/ML CMAX=PG/ML TMAX=HR

Table 12. LSMEANS AND 90% CONFIDENCE INTERVALS

	LSMEAN1	LSMEAN2	LOWCI12	UPPCI12
PARAMETER				
AUCI	695.42	407.07	70.94	270.73
AUCT	632.72	444.25	75.17	209.67
CMAX	698.70	645.92	78.60	137.75
LAUCI	310.10	322.75	84.28	109.53
LAUCT	266.59	270.30	85.42	113.87
LCMAX	363.17	396.66	78.09	107.35

LSMEAN1=LSMEAN FOR THE TEST PRODUCT
LSMEAN2=LSMEAN FOR THE REFERENCE PRODUCT
LOWCI12=LOWER 90% CONFIDENCE INTERVAL
UPPCI12=UPPER 90% CONFIDENCE INTERVAL

(c). Test/Reference ratios for individual subjects

Table 13 shows the test/reference ratios of pharmacokinetic parameters for 29 individuals. The variability (CV) of the ratios for the AUC_t, AUC_i and C_{max} was in the range of 100%, which is extremely high. Statistics of the ratios are shown in Table 14.

Table 13. Test Product/Reference Product Ratios for Individual Subjects

OBS	SUB	SEQ	RAUCT12	RAUCI12	RCMAX12	RTMAX12	RKE12	RTHALF12
1	1	2						
2	2	1						
3	3	2						
4	9	1						
5	10	2						
6	11	1						
7	12	2						
8	13	1						
9	14	2						
10	15	2						
11	16	1						
12	18	1						
13	19	2						
14	22	1						
15	23	2						
16	24	1						
17	25	1						
18	26	2						
19	27	2						
20	28	1						
21	29	1						
22	31	2						
23	32	1						
24	33	1						
25	34	2						
26	35	1						
27	37	1						
28	38	2						
29	39	2						

Table 14. Statistics on the Test/Reference Ratios

Variable	N	Mean	Std Dev	Minimum	Maximum
RAUCT12	29	1.35	1.30		
RAUCI12	22	1.20	1.02		
RCMAX12	29	1.21	1.12		
RTMAX12	29	1.11	0.36		
RKE12	22	1.07	0.49		
RTHALF12	22	1.21	0.73		

2. Amphetamine

Subject 18 was removed from the data analysis by the reviewer because the plasma levels for the test product showed only three non-zero blood levels out of 18 sampling time points. A total of 38 subjects were used in the amphetamine data analysis.

(a). Mean plasma levels

Both the test and reference products showed similar plasma-time profiles as indicated by the mean plasma amphetamine level at each sampling time point and the test/reference ratio as shown in Table 15 and Figure 2. The magnitude of the inter-subject variability was also comparable. The peaks of the plasma amphetamine-time profiles were 2.66 ng/mL (%CV=25) and 2.60 ng/mL (%CV=20) occurred at 3 hours for the test and reference products, respectively.

The plasma amphetamine levels for the test and reference products formed a plateau stretching over approximately 15 hours starting 1 hour time point. The half-life was approximately 19 hours for both products.

Significant sequence effects were detected at 2-24 hours and significant treatment effects were detected at 12, 24, and 48 hours. No significant period effects were detected.

Table 15. MEAN PLASMA AMPHETAMINE LEVELS FOR TEST AND REFERENCE PRODUCTS (N=38, Unit=ng/mL)

	MEAN1	SD1	MEAN2	SD2	RMEAN12
TIME HR					
0	0.00	0.00	0.00	0.00	.
0.25	0.01	0.07	0.00	0.00	.
0.5	0.17	0.30	0.29	0.30	0.58
0.75	0.84	0.60	1.01	0.52	0.83
1	1.43	0.71	1.60	0.59	0.90
1.25	1.86	0.78	2.00	0.59	0.93
1.5	2.12	0.78	2.25	0.61	0.94
2	2.44	0.73	2.48	0.54	0.98
3	2.66	0.66	2.60	0.51	1.02
4	2.55	0.57	2.59	0.49	0.99
6	2.45	0.48	2.58	0.45	0.95
8	2.51	0.51	2.58	0.42	0.97
12	2.16	0.42	2.29	0.43	0.94
16	2.02	0.47	2.11	0.37	0.96
24	1.42	0.39	1.55	0.38	0.92
48	0.52	0.26	0.59	0.25	0.87
72	0.15	0.21	0.15	0.22	1.01
96	0.02	0.09	0.01	0.07	2.19

MEAN1=TEST PRODUCT
MEAN2=REFERENCE PRODUCT
SD1=STANDARD DEVIATION FOR THE TEST PRODUCT
SD2=STANDARD DEVIATION FOR THE REFERENCE PRODUCT
RMEAN12=TEST MEAN/REFERENCE MEAN RATIO

(b). Pharmacokinetic parameters

The pharmacokinetic parameters, AUC_t, AUC_i and C_{max}, were comparable for both the test and reference products. Variability was also comparable and ranged 19-28% CV. The test/reference ratios were all within 0.94-0.99 for the log/non-transformed parameters as shown in Table 16. The 90% CI's for the log-transformed AUC_t, AUC_i and C_{max} were all within the 80-125% requirement as shown in Table 17.

Significant treatment effect was detected with AUC_i and significant sequence effects were detected with AUC_i, C_{max}, $LAUC_t$, $LAUC_i$ and LC_{max}. No significant period effects were detected.

Table 16. TEST MEAN/REFERENCE MEAN RATIOS (*ANTILOG CONVERSION)

	MEAN1	SD1	MEAN2	SD2	RMEAN12
PARAMETER					
AUCI	91.12	22.80	95.67	21.71	0.95
AUCT	77.35	22.04	82.02	20.60	0.94
CMAX	2.88	0.68	2.91	0.52	0.99
LAUCI*	88.49	0.24	93.35	0.22	0.95
LAUCT*	74.40	0.28	79.43	0.26	0.94
LCMAX*	2.80	0.23	2.87	0.18	0.98

UNIT: AUC=NG HR/ML CMAX=NG/ML TMAX=HR

Table 17. LSMEANS AND 90% CONFIDENCE INTERVALS

	LSMEAN1	LSMEAN2	LOWCI12	UPPCI12
PARAMETER				
AUCI	91.39	96.01	91.25	99.12
AUCT	77.61	82.30	89.06	99.54
CMAX	2.89	2.92	93.26	104.24
LAUCI	88.76	93.72	90.95	98.63
LAUCT	74.65	79.73	88.08	99.54
LCMAX	2.81	2.88	92.76	102.98

LSMEAN1=LSMEAN FOR THE TEST PRODUCT
LSMEAN2=LSMEAN FOR THE REFERENCE PRODUCT
LOWCI12=LOWER 90% CONFIDENCE INTERVAL
UPPCI12=UPPER 90% CONFIDENCE INTERVAL

(c). Test/Reference ratios for individual subjects

The test/reference ratios for the AUC_t, AUC_i and C_{max} for individual subjects are listed in Table 18 and their statistics are summarized in Table 19. Means of the ratios for the AUC_t, AUC_i and C_{max} are all within 0.96-1.0 with a CV of 14-20%.

Table 18. Test Product/Reference Product Ratios for IndividualSubjects

OBS	SUB	SEQ	RAUCT12	RAUCI12	RCMAX12	RTMAX12	RKE12	RTHALF12
1	1	2						
2	2	1						
3	3	2						
4	4	1						
5	5	2						
6	6	1						
7	7	2						
8	8	1						
9	9	1						
10	10	2						
11	11	1						
12	12	2						
13	13	1						
14	14	2						
15	15	2						
16	16	1						
17	17	2						
18	19	2						
19	21	2						
20	22	1						
21	23	2						
22	24	1						
23	25	1						
24	26	2						
25	27	2						
26	28	1						
27	29	1						
28	30	2						
29	31	2						
30	32	1						
31	33	1						
32	34	2						
33	35	1						
34	36	2						
35	37	1						
36	38	2						
37	39	2						
38	40	1						

Table 19. Statistics on the Test/Reference Ratios

Variable	N	Mean	Std Dev	Minimum	Maximum
RAUCT12	38	0.96	0.20		
RAUCI12	38	0.96	0.13		
RCMAX12	38	1.00	0.20		
RTMAX12	38	1.14	0.87		
RKE12	38	1.02	0.23		

RTHALF12 38

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3. Methamphetamine

Thirty-nine subjects were used to perform the methamphetamine data analysis.

(a). Mean plasma levels

Both the test and reference products showed similar plasma-time profiles as indicated by the mean plasma methamphetamine level at each sampling time point and the test/reference ratio as shown in Table 20 and Figure 3. The magnitude of the inter-subject variability was also comparable. The peaks of the plasma methamphetamine-time profiles were 10.64 ng/mL (%CV=17) and 10.94 ng/mL (%CV=16) occurred at 3 hours for the test product and at 2 hours for the reference product, respectively.

The plasma methamphetamine levels for the test and reference products formed a plateau stretching over approximately 5 hours starting 1 hour time point. The half-life was approximately 15 hours for both products.

Significant sequence effect was detected at 2 hours and period effects were detected at 4 and 72 hours. Significant treatment effects were detected at 8-24 hours.

Table 20. MEAN PLASMA METHAMPHETAMINE LEVELS FOR TEST AND REFERENCE PRODUCTS (N=39, Unit=ng/mL)

	MEAN1	SD1	MEAN2	SD2	RMEAN12
TIME HR					
0	0.00	0.00	0.00	0.00	.
0.25	0.02	0.07	0.02	0.10	0.67
0.5	1.10	1.33	1.42	1.35	0.77
0.75	4.02	2.67	4.78	2.57	0.84
1	6.61	2.83	7.33	2.41	0.90
1.25	8.52	2.84	9.16	2.39	0.93
1.5	9.44	2.55	10.19	2.11	0.93
2	10.53	2.15	10.94	1.78	0.96
3	10.64	1.83	10.76	1.68	0.99
4	10.01	1.67	10.36	1.58	0.97
6	9.17	1.61	9.51	1.50	0.96
8	8.70	1.76	9.24	1.71	0.94
12	7.09	1.49	7.41	1.38	0.96
16	6.19	1.51	6.53	1.43	0.95
24	3.99	1.09	4.25	1.19	0.94
48	1.27	0.60	1.40	0.63	0.91
72	0.44	0.38	0.49	0.39	0.90
96	0.14	0.21	0.13	0.21	1.03

MEAN1=TEST PRODUCT
MEAN2=REFERENCE PRODUCT
SD1=STANDARD DEVIATION FOR THE TEST PRODUCT
SD2=STANDARD DEVIATION FOR THE REFERENCE PRODUCT
RMEAN12=TEST MEAN/REFERENCE MEAN RATIO

(b). Pharmacokinetic parameters

The pharmacokinetic parameters, AUC_t, AUC_i and C_{max}, were comparable for both the test and reference products. Variability was also comparable and ranged 16-26% CV. The test/reference ratios were all within 0.94-0.98 for the log/non-transformed parameters as shown in Table 21. The 90% CI's for the log-transformed AUC_t, AUC_i and C_{max} were all within the 80-125% requirement as shown in Table 22.

Significant treatment effects were detected with log/non-transformed AUC_t and AUC_i and sequence effects were detected with log/non-transformed C_{max}.

Table 21. TEST MEAN/REFERENCE MEAN RATIOS (*ANTILOG CONVERSION)

	MEAN1	SD1	MEAN2	SD2	RMEAN12
PARAMETER					
AUCI	264.95	68.17	281.42	67.40	0.94
AUCT	254.71	65.70	269.83	65.62	0.94
CMAX	11.36	2.19	11.59	1.82	0.98
LAUCI*	255.65	0.28	273.10	0.25	0.94
LAUCT*	245.63	0.28	261.63	0.26	0.94
LCMAX*	11.15	0.19	11.46	0.16	0.97

UNIT: AUC=PG HR/ML CMAX=PG/ML TMAX=HR

Table 22. LSMEANS AND 90% CONFIDENCE INTERVALS

	LSMEAN1	LSMEAN2	LOWCI12	UPPCI12
PARAMETER				
AUCI	265.09	281.74	90.72	97.46
AUCT	254.85	270.15	90.87	97.80
CMAX	11.37	11.61	93.66	102.28
LAUCI	255.85	273.47	90.35	96.88
LAUCT	245.83	262.00	90.49	97.30
LCMAX	11.16	11.47	93.18	101.67

LSMEAN1=LSMEAN FOR THE TEST PRODUCT
LSMEAN2=LSMEAN FOR THE REFERENCE PRODUCT
LOWCI12=LOWER 90% CONFIDENCE INTERVAL
UPPCI12=UPPER 90% CONFIDENCE INTERVAL

(c). Test/Reference ratios for individual subjects

The test/reference ratios for the AUC_t, AUC_i and C_{max} for individual subjects are listed in Table 23 and their statistics are summarized in Table 24. Means of the ratios for the AUC_t, AUC_i and C_{max} are all within 0.94-0.99 with a CV of 13-16%.

Table 23. Test Product/Reference Product Ratios for IndividualSubjects

OBS	SUB	SEQ	RAUCT12	RAUCI12	RCMAX12	RTMAX12	RKE12	RTHALF12
1	1	2						
2	2	1						
3	3	2						
4	4	1						
5	5	2						
6	6	1						
7	7	2						
8	8	1						
9	9	1						
10	10	2						
11	11	1						
12	12	2						
13	13	1						
14	14	2						
15	15	2						
16	16	1						
17	17	2						
18	18	1						
19	19	2						
20	21	2						
21	22	1						
22	23	2						
23	24	1						
24	25	1						
25	26	2						
26	27	2						
27	28	1						
28	29	1						
29	30	2						
30	31	2						
31	32	1						
32	33	1						
33	34	2						
34	35	1						
35	36	2						
36	37	1						
37	38	2						
38	39	2						
39	40	1						

Table 24. Statistics on the Test/Reference Ratios

Variable	N	Mean	Std Dev	Minimum	Maximum
RAUCT12	39	0.95	0.13		
RAUCI12	39	0.94	0.12		
RCMAX12	39	0.99	0.16		
RTMAX12	39	1.40	1.16		
RKE12	39	1.04	0.15		
RTHALF12	39	0.99	0.15		

4. Desmethylselegiline

Thirty-nine subjects were used to perform the desmethylselegiline data analysis.

(a). Mean plasma levels

Both the test and reference products showed similar plasma-time profiles as indicated by the mean plasma desmethylselegiline level at each sampling time point and the test/reference ratio as shown in Table 25 and Figure 4. The magnitude of the inter-subject variability was also comparable. The peaks of the plasma desmethylselegiline-time profiles were 10.26 ng/mL (%CV=47) and 11.02 ng/mL (%CV=39) occurred at 0.75 hour for the test product and the reference product, respectively.

The plasma desmethylselegiline levels for the test and reference products did not form a plateau as observed with amphetamine and methamphetamine profiles. The half-life was approximately 3.3 hours for the test product and 4 hours for the reference product.

Significant treatment effect was detected only at 0.25 hour. Significant sequence effects were detected at 1.5 hours and 2 hours. Significant period effects were detected at 1-16 hours.

Table 25. MEAN PLASMA DESMETHYLSELEGILINE LEVELS FOR TEST AND REFERENCE PRODUCTS

(N=39, Unit=ng/mL)

	MEAN1	SD1	MEAN2	SD2	RMEAN12
TIME HR					
0	0.00	0.00	0.00	0.00	.
0.25	0.47	0.82	0.95	1.35	0.49
0.5	5.64	4.16	7.26	6.07	0.78
0.75	10.26	4.80	11.02	4.27	0.93
1	9.80	3.60	10.36	3.43	0.95
1.25	8.90	2.65	9.11	3.47	0.98
1.5	7.98	2.33	7.92	3.31	1.01
2	5.54	2.07	5.45	2.28	1.02
3	3.00	1.42	2.82	1.33	1.06
4	1.80	0.80	1.82	0.92	0.99
6	0.88	0.46	0.91	0.47	0.98
8	0.55	0.33	0.54	0.32	1.02
12	0.20	0.24	0.20	0.28	1.02
16	0.05	0.15	0.09	0.17	0.61
24	0.03	0.10	0.06	0.13	0.58
48	0.02	0.10	0.01	0.06	1.20
72	0.00	0.00	0.00	0.00	.
96	0.00	0.00	0.01	0.04	0.00

MEAN1=TEST PRODUCT
MEAN2=REFERENCE PRODUCT
SD1=STANDARD DEVIATION FOR THE TEST PRODUCT
SD2=STANDARD DEVIATION FOR THE REFERENCE PRODUCT
RMEAN12=TEST MEAN/REFERENCE MEAN RATIO

(b). Pharmacokinetic parameters

The pharmacokinetic parameters, AUC_t, AUC_i and C_{max}, were comparable for both the test and reference products. Variability was also comparable and ranged 38-46% CV. The test/reference ratios were all within 0.93-0.98 for the log/non-transformed parameters as shown in Table 26. The 90% CI's for the log-transformed AUC_t, AUC_i and C_{max} were all within the 80-125% requirement as shown in Table 27.

No significant treatment and sequence effects were detected. However, significant period effects were detected with AUC_t, AUC_i, $LAUC_t$, $LAUC_i$ and Lc_{max}.

Table 26. TEST MEAN/REFERENCE MEAN RATIOS (*ANTILOG CONVERSION)

	MEAN1	SD1	MEAN2	SD2	RMEAN12
PARAMETER					
AUCI	27.67	11.28	28.87	13.31	0.96
AUCT	25.84	10.02	26.96	11.94	0.96
CMAX	11.71	3.53	12.65	4.79	0.93
LAUCI*	25.78	0.37	26.36	0.42	0.98
LAUCT*	24.21	0.36	24.73	0.42	0.98
LCMAX*	11.18	0.31	11.88	0.36	0.94

UNIT: AUC=PG HR/ML CMAX=PG/ML TMAX=HR

Table 27. LSMEANS AND 90% CONFIDENCE INTERVALS

	LSMEAN1	LSMEAN2	LOWCI12	UPPCI12
PARAMETER				
AUCI	27.63	28.97	85.59	105.16
AUCT	25.81	27.05	87.70	103.10
CMAX	11.71	12.68	83.64	101.05
LAUCI	25.76	26.45	89.96	105.40
LAUCT	24.19	24.82	91.05	104.30
LCMAX	11.17	11.91	86.65	101.59

LSMEAN1=LSMEAN FOR THE TEST PRODUCT
LSMEAN2=LSMEAN FOR THE REFERENCE PRODUCT
LOWCI12=LOWER 90% CONFIDENCE INTERVAL
UPPCI12=UPPER 90% CONFIDENCE INTERVAL

(c). Test/Reference ratios for individual subjects

The test/reference ratios for the AUC_t, AUC_i and C_{max} for individual subjects are listed in Table 28 and their statistics are summarized in Table 29. Means of the ratios for the AUC_t, AUC_i and C_{max} are all within 0.94-0.99 with a CV of 13-16%.

Table 28. Test Product/Reference Product Ratios for IndividualSubjects

OBS	SUB	SEQ	RAUCT12	RAUCI12	RCMAX12	RTMAX12	RKE12	RTHALF12
1	1	2						
2	2	1						
3	3	2						
4	4	1						
5	5	2						
6	6	1						
7	7	2						
8	8	1						
9	9	1						
10	10	2						
11	11	1						
12	12	2						
13	13	1						
14	14	2						
15	15	2						
16	16	1						
17	17	2						
18	18	1						
19	19	2						
20	21	2						
21	22	1						
22	23	2						
23	24	1						
24	25	1						
25	26	2						
26	27	2						
27	28	1						
28	29	1						
29	30	2						
30	31	2						
31	32	1						
32	33	1						
33	34	2						
34	35	1						
35	36	2						
36	37	1						
37	38	2						
38	39	2						
39	40	1						

Table 29. Statistics on the Test/Reference Ratios

Variable	N	Mean	Std Dev	Minimum	Maximum
RAUCT12	39	0.95	0.13		
RAUCI12	39	0.94	0.12		
RCMAX12	39	0.99	0.16		
RTMAX12	39	1.40	1.16		
RKE12	39	1.04	0.15		
RTHALF12	39	0.99	0.15		

B. Study under Nonfasting Conditions

A total of 20 healthy male subjects participated in the study and 18 subjects completed the nonfasting study. Subject #10 voluntarily withdrew from the study following Period 1 and Subject #16 was discontinued from the study during Period 1 due to illness (otitis media).

There were no clinically significant abnormal laboratory values or significant changes in the vital signs during the course of the study.

A total of 26 adverse events (paresthesia, dizziness, syncope, headache, rash, etc.) were reported by 12 subjects. All events (14 events for the test product under fasting conditions, 6 events for the test product under food conditions and 6 events for the reference product under food conditions) were not serious and no subjects were withdrawn from the study because of the adverse events except Subject #16 who was discontinued from the study due to otitis media.

Data for the plasma levels, pharmacokinetic parameters and the statistical analyses were summarized for each of the parent drug and its three metabolites.

1. Selegiline

The plasma levels of selegiline were so low with three subjects that the data from those subjects were removed from the statistical analyses by the reviewer. Three subjects registered only three or fewer than three non-zero plasma selegiline levels out of 13 sampling time points. Table 30 summarizes those subjects. A total of 15 subjects were used to analyze the plasma levels and pharmacokinetic parameters of selegiline.

The C_{max} for amphetamine submitted in the data diskette (file name=amphet\params.prn) were different up to 30% from the C_{max} in the plasma data file (file name=amphet\concs.prn). The sponsor did not explain about this discrepancy in the submission.

The data analysis in this review for the selegiline and all three metabolites were based on the correct data.

Table 30. Subjects Showing Non-zero Selegiline Levels
Food Study

No. of Non-zero Levels	Subject # Test Product	Ref Product	Total
0	-	-	0
1	6(test-fast)	-	1
2	2(test-food)	3(ref-food)	2
3	-	-	0
4 or more	-	-	15

(a). Mean plasma levels

Table 31 shows that the plasma selegiline levels under food conditions are much higher resulting in higher AUC and C_{max} as compared to the dosing under fasting conditions. The inter-subject variability is also extremely high for the plasma selegiline levels under fasting and food conditions. The peaks of the mean plasma levels were 390 pg/mL (%CV=77) at 0.75 hour for the test product under fasting conditions, 635 pg/mL (%CV=174) at 1 hour for the test product under food conditions, and 487 pg/mL (%CV=134) at 1.25 hours for the reference product under food conditions. It appears that there is a food effect with regard to the plasma selegiline level-time profiles.

Table 31. MEAN PLASMA SELEGILINE LEVELS FOR TEST AND REFERENCE PRODUCTS (N=15, Unit=pg/mL)

	MEAN1	SD1	MEAN2	SD2	MEAN3
TIME HR					
0	0.00	0.00	0.00	0.00	0.00
0.25	20.26	52.60	11.15	26.13	45.83
0.5	207.50	121.36	286.47	513.70	348.43
0.75	390.07	298.99	444.46	435.50	451.71
1	248.07	229.82	634.73	1106.47	459.31
1.25	192.05	277.17	388.57	333.69	487.17
1.5	150.27	219.86	397.25	368.80	359.41
2	77.37	102.87	241.35	288.84	318.23
2.5	38.67	63.93	150.80	172.75	260.45
3	16.65	36.05	90.45	127.54	230.25
4	10.06	25.28	41.41	72.54	130.39
6	3.11	12.03	10.97	29.15	37.87
8	2.77	10.72	5.81	16.88	26.67

(CONTINUED)

	SD3	RMEAN12	RMEAN13	RMEAN23
TIME HR				
0	0.00	.	.	.
0.25	65.39	1.82	0.44	0.24
0.5	314.90	0.72	0.60	0.82
0.75	617.82	0.88	0.86	0.98
1	558.55	0.39	0.54	1.38
1.25	650.96	0.49	0.39	0.80
1.5	435.19	0.38	0.42	1.11
2	467.36	0.32	0.24	0.76
2.5	436.47	0.26	0.15	0.58
3	491.83	0.18	0.07	0.39
4	282.10	0.24	0.08	0.32
6	101.99	0.28	0.08	0.29
8	72.14	0.48	0.10	0.22

MEAN1=TEST PRODUCT UNDER FASTING
MEAN2=TEST PRODUCT UNDER FOOD
MEAN3=REFERENCE PRODUCT UNDER FOOD
RMEAN12=TEST MEAN UNDER FASTING/TEST MEAN UNDER FOOD RATIO
RMEAN23=TEST MEAN/REFERENCE MEAN RATIO UNDER FOOD

(b). Pharmacokinetic parameters

Table 32 shows that the inter-subject variability for the pharmacokinetic parameters is extremely high. The %CV ranged 70-157. The ratio of test under fast/test under food (RMEAN12) indicates that there are food effects. The parameters under food conditions are as two-fold larger as the parameters under fasting conditions. The test/reference ratios under food conditions (RMEAN23) range 0.7-1.48.

Table 32. TEST MEAN/REFERENCE MEAN RATIOS (*ANTILOG CONVERSION)

	MEAN1	SD1	MEAN2	SD2	MEAN3
PARAMETER					
AUCI	471.43	481.42	1041.15	953.23	1452.39
AUCT	402.91	455.84	917.78	937.20	1310.62
CMAX	412.00	290.58	890.47	1128.24	603.00
LAUCI*	372.09	0.61	784.37	0.73	730.15
LAUCT*	297.82	0.71	626.29	0.89	638.75
LCMAX*	341.86	0.62	552.55	0.95	427.72

(CONTINUED)

	SD3	RMEAN12	RMEAN13	RMEAN23
PARAMETER				
AUCI	2293.52	0.45	0.32	0.72
AUCT	2127.32	0.44	0.31	0.70
CMAX	653.12	0.46	0.68	1.48
LAUCI	1.06	0.47	0.51	1.07
LAUCT	1.07	0.48	0.47	0.98
LCMAX	0.76	0.62	0.80	1.29

UNIT: AUC=PG HR/ML CMAX=PG/ML TMAX=HR

(c). Test/Reference ratios for individual subjects

The test/reference ratios for the individual subjects are listed in Table 33 and their statistics are summarized in Table 34. The test/reference ratios under food conditions (RAUCT23, RAUCI23, and RCMAX23) and their standard deviations indicate a high variability.

Table 33. Test Product/Reference Product Ratios for Individual Subjects

OBS	SUB	SEQ	RAUCT12	RAUCI12	RCMAX12	RTMAX12	RKE12	RTHALF12	RAUCT13	RAUCI13	RCMAX13
1	1	4									
2	4	5									
3	5	6									
4	7	5									
5	8	4									
6	9	2									
7	11	3									
8	12	6									
9	13	6									
10	14	4									
11	15	5									
12	17	1									
13	18	3									
14	19	4									
15	20	5									

OBS	RTMAX13	RKE13	RTHALF13	RAUCT23	RAUCI23	RCMAX23	RTMAX23	RKE23	RTHALF23
1									
2									
3									
4									
5									
6									
7									
8									
9									
10									
11									
12									
13									
14									
15									

Table 34. Statistics on the Test/Reference Ratios

Variable	N	Mean	Std Dev	Minimum	Maximum
RAUCT12	15	0.63	0.61		
RAUCI12	14	0.54	0.25		
RCMAX12	15	0.98	1.16		
RTMAX12	15	0.82	0.31		
RKE12	14	1.26	1.15		
RTHALF12	14	1.49	1.03		
RAUCT13	15	0.60	0.43		
RAUCI13	15	0.64	0.42		
RCMAX13	15	1.10	0.93		
RTMAX13	15	0.82	0.42		
RKE13	15	1.60	1.64		
RTHALF13	15	1.76	2.55		
RAUCT23	15	1.12	0.60		
RAUCI23	14	1.14	0.63		
RCMAX23	15	1.64	1.43		
RTMAX23	15	1.07	0.56		
RKE23	14	1.59	1.75		
RTHALF23	14	1.14	0.90		

2. Amphetamine

A total of 18 subjects were used for the data analysis.

(a). Mean plasma levels

All the three plasma amphetamine-time profiles, the test product under fasting conditions and the test and reference products under food conditions, were similar as indicated by the mean plasma amphetamine level at each sampling time point and the test/test ratio or test/reference ratio. See Table 35. The magnitude of the inter-subject variability was also comparable for each of the three treatments. The peaks of the plasma amphetamine-time profiles were 2.72 ng/mL (%CV=33) at 8 hours for the test product under fasting conditions, 2.75 ng/mL (%CV=29) at 4 hours for the test product under food conditions and 2.85 ng/mL (%CV=31) at 6 hours for the reference product under food conditions.

The plasma amphetamine levels for all the three treatments formed a plateau stretching over approximately 15 hours starting 1.5 hours time point. The half-life was approximately 16-20 hours.

No significant sequence and period effects were detected at all

sampling time points. Treatment effects were detected only at 1 and 1.25 hours.

Table 35. MEAN PLASMA AMPHETAMINE LEVELS FOR TEST AND REFERENCE PRODUCTS (N=18, Unit=ng/mL)

	MEAN1	SD1	MEAN2	SD2	MEAN3
TIME HR					
0	0.00	0.00	0.00	0.00	0.00
0.25	0.00	0.00	0.00	0.00	0.00
0.5	0.15	0.21	0.07	0.18	0.22
0.75	0.83	0.35	0.56	0.81	0.63
1	1.30	0.40	0.88	0.66	0.97
1.25	1.76	0.52	1.19	0.78	1.26
1.5	2.03	0.57	1.48	0.85	1.56
2	2.38	0.56	1.92	0.75	1.91
3	2.55	0.63	2.66	0.75	2.39
4	2.67	0.88	2.75	0.80	2.61
6	2.68	0.83	2.72	0.73	2.85
8	2.72	0.91	2.62	0.79	2.83
12	2.29	0.74	2.32	0.77	2.56
16	1.88	0.59	2.02	0.58	1.99
24	1.40	0.50	1.49	0.50	1.43
48	0.62	0.44	0.57	0.35	0.50
72	0.14	0.36	0.16	0.25	0.12
96	0.04	0.17	0.02	0.08	0.02

(CONTINUED)

	SD3	RMEAN12	RMEAN13	RMEAN23
TIME HR				
0	0.00	.	.	.
0.25	0.00	.	.	.
0.5	0.29	2.19	0.68	0.31
0.75	0.63	1.48	1.32	0.90
1	0.66	1.48	1.34	0.91
1.25	0.84	1.48	1.39	0.94
1.5	0.90	1.37	1.30	0.95
2	0.92	1.24	1.24	1.00
3	0.82	0.96	1.07	1.11
4	0.82	0.97	1.02	1.06
6	0.87	0.99	0.94	0.95
8	0.77	1.04	0.96	0.93
12	1.48	0.99	0.90	0.91
16	0.59	0.93	0.95	1.02
24	0.52	0.94	0.97	1.04
48	0.28	1.09	1.24	1.14
72	0.24	0.85	1.16	1.36
96	0.08	2.09	2.21	1.06

MEAN1=TEST PRODUCT UNDER FASTING
MEAN2=TEST PRODUCT UNDER FOOD
MEAN3=REFERENCE PRODUCT UNDER FOOD
RMEAN12=TEST MEAN UNDER FASTING/TEST MEAN UNDER FOOD RATIO
RMEAN23=TEST MEAN/REFERENCE MEAN RATIO UNDER FOOD

(b). Pharmacokinetic parameters

The pharmacokinetic parameters, AUC_t, AUC_i and C_{max}, were comparable for the three treatments. Variability was also comparable and ranged 30-50% CV. The test/reference ratios under food conditions (RMEAN23) were all within 0.89-1.04 for the log/non-transformed parameters as shown in Table 36 and met the requirement of the Division.

No significant sequence, period and treatment effects were detected for the log/non-transformed AUC_t, AUC_i and C_{max}.

Table 36. TEST MEAN/REFERENCE MEAN RATIOS (*ANTILOG CONVERSION)

PARAMETER	MEAN1	SD1	MEAN2	SD2	MEAN3
AUCI	94.61	44.44	91.38	33.69	87.82
AUCT	79.86	39.62	81.33	33.14	79.19
CMAX	2.94	0.94	3.00	0.91	3.39
LAUCI*	87.29	0.41	85.13	0.41	82.80
LAUCT*	71.70	0.51	73.42	0.53	74.01
LCMAX*	2.78	0.37	2.84	0.37	3.15

(CONTINUED)

PARAMETER	SD3	RMEAN12	RMEAN13	RMEAN23
AUCI	31.54	1.04	1.08	1.04
AUCT	30.72	0.98	1.01	1.03
CMAX	1.46	0.98	0.87	0.89
LAUCI	0.36	1.03	1.05	1.03
LAUCT	0.38	0.98	0.97	0.99
LCMAX	0.38	0.98	0.88	0.90

UNIT: AUC=NG HR/ML CMAX=NG/ML TMAX=HR

(c). Test/Reference ratios for individual subjects

The test/reference ratios for the individual subjects are listed in Table 37 and their statistics are summarized in Table 38. The means of the test/reference ratios under food conditions (RAUCT23, RAUCI23, and RCMAX23) are within 0.95-1.06 and their standard deviations are within 0.28-0.35.

Table 37. Test Product/Reference Product Ratios for Individual Subjects

OBS	SUB	SEQ	RAUCT12	RAUCI12	RCMAX12	RTMAX12	RKE12	RTHALF12	RAUCT13	RAUCI13	RCMAX13
1	1	4									
2	2	3									
3	3	2									
4	4	5									
5	5	6									
6	6	1									
7	7	5									
8	8	4									
9	9	2									
10	11	3									
11	12	6									
12	13	6									
13	14	4									
14	15	5									
15	17	1									
16	18	3									
17	19	4									
18	20	5									

OBS	RTMAX13	RKE13	RTHALF13	RAUCT23	RAUCI23	RCMAX23	RTMAX23	RKE23	RTHALF23
1									
2									
3									
4									
5									
6									
7									
8									
9									
10									
11									
12									

Table 38. Statistics on the Test/Reference Ratios

Variable	N	Mean	Std Dev	Minimum	Maximum
RAUCT12	18	0.99	0.16		
RAUCI12	18	1.05	0.23		
RCMAX12	18	0.99	0.15		
RTMAX12	18	1.21	0.91		
RKE12	18	0.95	0.24		
RTHALF12	18	1.13	0.32		
RAUCT13	18	1.01	0.30		
RAUCI13	18	1.09	0.28		
RCMAX13	18	0.95	0.38		
RTMAX13	18	0.91	0.36		
RKE13	18	0.85	0.26		
RTHALF13	18	1.35	0.67		
RAUCT23	18	1.04	0.35		
RAUCI23	18	1.06	0.29		
RCMAX23	18	0.95	0.28		
RTMAX23	18	0.98	0.58		
RKE23	18	0.91	0.26		
RTHALF23	18	1.23	0.57		

3. Methamphetamine

A total of 18 subjects were used for the data analysis.

(a). Mean plasma levels

All the three treatments showed similar plasma-time profiles as indicated by the mean plasma methamphetamine level at each sampling time point and the test/test and test/reference ratios. The magnitude of the inter-subject variability was also comparable. The peaks of the plasma methamphetamine-time profiles were 9.99 ng/mL (%CV=19) at 3 hours for the test product under fasting conditions, 10.83 ng/mL (%CV=23) at 4 hours for the test product under food conditions and 10.03 ng/mL (%CV=24) at 4 hours for the reference product under food conditions.

The plasma methamphetamine levels for the three treatments formed a plateau stretching over approximately 6 hours starting 2 hour time point. The half-life was approximately 14-15 hours.

No significant sequence, period and treatment effects were detected at all the sampling time points.

Table 39. MEAN PLASMA METHAMPHETAMINE LEVELS FOR TEST AND REFERENCE PRODUCTS (N=18, Unit=ng/mL)

	MEAN1	SD1	MEAN2	SD2	MEAN3
TIME HR					
0	0.00	0.00	0.00	0.00	0.02
0.25	0.00	0.00	0.00	0.00	0.04
0.5	0.91	0.78	0.65	1.02	1.31
0.75	3.85	1.83	2.47	2.02	3.16
1	5.92	2.01	4.64	3.03	4.58
1.25	7.66	2.39	5.87	3.57	5.84
1.5	8.70	2.09	6.82	3.46	6.91
2	9.94	2.07	8.49	2.92	8.21
3	9.99	1.94	10.81	2.67	9.68
4	9.85	3.08	10.83	2.49	10.03
6	9.08	2.50	9.50	2.21	9.57
8	8.41	2.73	8.64	2.18	9.13
12	6.44	2.07	6.66	1.88	6.67
16	4.93	1.58	5.29	1.69	5.24
24	3.23	1.48	3.46	1.45	3.36
48	1.14	1.09	1.09	0.87	1.00
72	0.40	0.77	0.35	0.49	0.32
96	0.10	0.36	0.05	0.19	0.06

(CONTINUED)

	SD3	RMEAN12	RMEAN13	RMEAN23
TIME HR				
0	0.09	.	0.00	0.00
0.25	0.17	.	0.00	0.00
0.5	1.24	1.41	0.70	0.49
0.75	2.65	1.56	1.22	0.78
1	2.71	1.28	1.29	1.01
1.25	3.28	1.31	1.31	1.01
1.5	3.26	1.28	1.26	0.99
2	3.15	1.17	1.21	1.03
3	2.77	0.92	1.03	1.12
4	2.40	0.91	0.98	1.08
6	2.07	0.96	0.95	0.99
8	2.34	0.97	0.92	0.95
12	1.79	0.97	0.97	1.00
16	1.75	0.93	0.94	1.01
24	1.56	0.93	0.96	1.03
48	0.77	1.04	1.14	1.09
72	0.48	1.14	1.23	1.08
96	0.18	2.19	1.71	0.78

MEAN1=TEST PRODUCT UNDER FASTING
MEAN2=TEST PRODUCT UNDER FOOD
MEAN3=REFERENCE PRODUCT UNDER FOOD
RMEAN12=TEST MEAN UNDER FASTING/TEST MEAN UNDER FOOD RATIO
RMEAN23=TEST MEAN/REFERENCE MEAN RATIO UNDER FOOD

(b). Pharmacokinetic parameters

The pharmacokinetic parameters, AUC_t, AUC_i and C_{max}, were comparable for the three treatments. Variability was also comparable and ranged 20-50% CV. The test/reference ratios under food conditions (RMEAN23) were all within 1.01-1.02 for the log/non-transformed parameters as shown in Table 40 and met the requirement of the Division.

No significant sequence, period and treatment effects were detected for the log/non-transformed AUC_t, AUC_i and C_{max}.

Table 40. TEST MEAN/REFERENCE MEAN RATIOS (*ANTILOG CONVERSION)

	MEAN1	SD1	MEAN2	SD2	MEAN3
PARAMETER					
AUCI	235.45	118.43	237.47	93.31	232.80
AUCT	223.39	106.96	226.68	89.58	222.72
CMAX	10.78	2.88	11.28	2.54	11.06
LAUCI*	219.34	0.35	224.80	0.32	222.76
LAUCT*	208.66	0.35	214.29	0.33	212.68
LCMAX*	10.45	0.25	11.00	0.24	10.85

(CONTINUED)

	SD3	RMEAN12	RMEAN13	RMEAN23
PARAMETER				
AUCI	87.13	0.99	1.01	1.02
AUCT	84.90	0.99	1.00	1.02
CMAX	2.26	0.96	0.97	1.02
LAUCI	0.28	0.98	0.98	1.01
LAUCT	0.29	0.97	0.98	1.01
LCMAX	0.20	0.95	0.96	1.01

UNIT: AUC=NG HR/ML CMAX=NG/ML TMAX=HR

(c). Test/Reference ratios for individual subjects

The test/reference ratios for the individual subjects are listed in Table 41 and their statistics are summarized in Table 42. The means of the test/reference ratios under food conditions (RAUCT23, RAUCI23, and RCMAX23) are 1.04 and their standard deviations are within 0.22-0.28.

Table 41. Test Product/Reference Product Ratios for Individual Subjects

OBS	SUB	SEQ	RAUCT12	RAUCI12	RCMAX12	RTMAX12	RKE12	RTHALF12	RAUCT13	RAUCI13	RCMAX13
1	1	4									
2	2	3									
3	3	2									
4	4	5									
5	5	6									
6	6	1									
7	7	5									
8	8	4									
9	9	2									
10	11	3									
11	12	6									
12	13	6									
13	14	4									
14	15	5									
15	17	1									
16	18	3									
17	19	4									
18	20	5									

OBS	RTMAX13	RKE13	RTHALF13	RAUCT23	RAUCI23	RCMAX23	RTMAX23	RKE23	RTHALF23
1									
2									
3									
4									
5									
6									
7									
8									
9									
10									
11									
12									
13									

Table 42. Statistics on the Test/Reference Ratios

Variable	N	Mean	Std Dev	Minimum	Maximum
RAUCT12	18	0.98	0.12		
RAUCI12	18	0.98	0.13		
RCMAX12	18	0.96	0.11		
RTMAX12	18	0.84	0.33		
RKE12	18	0.97	0.15		
RTHALF12	18	1.06	0.16		
RAUCT13	18	1.00	0.23		
RAUCI13	18	1.00	0.22		
RCMAX13	18	0.98	0.20		
RTMAX13	18	0.80	0.43		
RKE13	18	0.99	0.23		
RTHALF13	18	1.07	0.24		
RAUCT23	18	1.04	0.28		
RAUCI23	18	1.04	0.27		
RCMAX23	18	1.04	0.22		
RTMAX23	18	1.01	0.52		
RKE23	18	1.03	0.24		
RTHALF23	18	1.02	0.23		

4. Desmethylselegiline

A total of 18 subjects were used for the data analysis.

(a). Mean plasma levels

There were differences found among the three treatments in the plasma-time profiles as shown in Table 43. The peaks of the plasma desmethylselegiline-time profiles were 14 ng/mL (%CV=64) at 1 hour for the test product under fasting conditions, 8.33 ng/mL (%CV=36) at 1.5 hours for the test product under food conditions and 7 ng/mL (%CV=48) at 2 hours for the reference product under food conditions. The test/reference ratios under food conditions range 1.05-1.2 over 0.75-3 hour period after dosing. The half-life was approximately 3.4-4.5 hours.

Significant treatment effects were detected at 0.50-1.5, 3, 4, 8, and 12 hours. Significant period effects were detected at 3-16 hours and significant sequence effect was detected at 0.25 hour.

Table 43. MEAN PLASMA DESMETHYLSELEGILINE LEVELS FOR TEST AND REFERENCE PRODUCTS

(N=18, Unit=ng/mL)

	MEAN1	SD1	MEAN2	SD2	MEAN3
TIME HR					
0	0.00	0.00	0.00	0.00	0.00
0.25	0.55	0.78	0.18	0.39	0.72
0.5	6.28	3.61	2.93	2.61	3.92
0.75	13.71	5.64	6.16	3.87	5.86
1	14.03	8.94	7.87	4.07	6.67
1.25	11.30	5.63	8.15	3.43	6.94
1.5	9.69	5.00	8.33	3.04	6.93
2	7.11	3.88	7.74	3.29	7.01
3	3.73	2.27	5.61	3.03	5.03
4	2.45	1.66	3.91	2.85	4.01
6	1.29	0.93	1.67	1.20	1.68
8	0.75	0.60	1.06	0.85	1.16
12	0.31	0.37	0.49	0.48	0.48
16	0.18	0.29	0.22	0.34	0.36
24	0.05	0.14	0.08	0.15	0.13
48	0.00	0.00	0.00	0.00	0.00
72	0.00	0.00	0.02	0.07	0.00
96	0.00	0.00	0.00	0.00	0.00

(CONTINUED)

	SD3	RMEAN12	RMEAN13	RMEAN23
TIME HR				
0	0.00	.	.	.
0.25	1.51	3.01	0.76	0.25
0.5	2.67	2.14	1.60	0.75
0.75	3.62	2.23	2.34	1.05
1	3.28	1.78	2.10	1.18
1.25	3.31	1.39	1.63	1.17
1.5	2.65	1.16	1.40	1.20
2	3.35	0.92	1.01	1.10
3	2.94	0.66	0.74	1.12
4	2.92	0.63	0.61	0.98
6	1.14	0.77	0.77	0.99
8	1.00	0.71	0.64	0.91
12	0.47	0.64	0.66	1.03
16	0.60	0.82	0.51	0.62
24	0.26	0.59	0.35	0.58
48	0.00	.	.	.
72	0.00	0.00	.	.
96	0.00	.	.	.

MEAN1=TEST PRODUCT UNDER FASTING
MEAN2=TEST PRODUCT UNDER FOOD
MEAN3=REFERENCE PRODUCT UNDER FOOD
RMEAN12=TEST MEAN UNDER FASTING/TEST MEAN UNDER FOOD RATIO
RMEAN23=TEST MEAN/REFERENCE MEAN RATIO UNDER FOOD

(b). Pharmacokinetic parameters

The pharmacokinetic parameters, AUC_t, AUC_i and C_{max}, were comparable for the test and reference products under food conditions. Variability was also comparable and ranged 28-59% CV. The test/reference ratios under food conditions (RMEAN23) were all within 1.01-1.07 for the log/non-transformed parameters as shown in Table 44 and met the requirement of the Division.

No significant sequence effect was detected for the log/non-transformed AUC_t, AUC_i and C_{max}. Significant period effects were detected for the log/non-transformed AUC_t and AUC_i. Significant treatment effects were detected for the log/non-transformed C_{max}.

Table 44. TEST MEAN/REFERENCE MEAN RATIOS (*ANTILOG CONVERSION)

	MEAN1	SD1	MEAN2	SD2	MEAN3
PARAMETER					
AUCI	36.23	21.66	38.59	20.82	38.38
AUCT	34.44	20.67	36.83	20.14	35.57
CMAX	15.67	8.82	10.17	2.87	9.56
LAUCI*	31.56	0.52	34.20	0.49	34.07
LAUCT*	29.94	0.52	32.52	0.50	31.58
LCMAX*	14.06	0.46	9.76	0.30	9.13

(CONTINUED)

	SD3	RMEAN12	RMEAN13	RMEAN23
PARAMETER				
AUCI	22.81	0.94	0.94	1.01
AUCT	20.87	0.94	0.97	1.04
CMAX	3.09	1.54	1.64	1.06
LAUCI	0.46	0.92	0.93	1.00
LAUCT	0.47	0.92	0.95	1.03
LCMAX	0.30	1.44	1.54	1.07

UNIT: AUC=NG HR/ML CMAX=NG/ML TMAX=HR

(c). Test/Reference ratios for individual subjects

The test/reference ratios for the individual subjects are listed in Table 45 and their statistics are summarized in Table 46. The means of the test/reference ratios under food conditions (RAUCT23, RAUCI23, and RCMAX23) are within 1.05-1.11 and their standard deviations are within 0.34-0.39.

Table 45. Test Product/Reference Product Ratios for IndividualSubjects

OBS	SUB	SEQ	RAUCT12	RAUCI12	RCMAX12	RTMAX12	RKE12	RTHALF12	RAUCT13	RAUCI13	RCMAX13
1	1	4									
2	2	3									
3	3	2									
4	4	5									
5	5	6									
6	6	1									
7	7	5									
8	8	4									
9	9	2									
10	11	3									
11	12	6									
12	13	6									
13	14	4									
14	15	5									
15	17	1									
16	18	3									
17	19	4									
18	20	5									

OBS	RTMAX13	RKE13	RTHALF13	RAUCT23	RAUCI23	RCMAX23	RTMAX23	RKE23	RTHALF23
1									
2									
3									
4									
5									
6									
7									
8									
9									
10									
11									
12									

Table 46. Statistics on the Test/Reference Ratios

Variable	N	Mean	Std Dev	Minimum	Maximum
RAUCT12	18	0.95	0.24		
RAUCI12	18	0.95	0.24		
RCMAX12	18	1.54	0.65		
RTMAX12	18	0.78	0.34		
RKE12	18	1.09	0.39		
RTHALF12	18	1.03	0.33		
RAUCT13	18	1.01	0.43		
RAUCI13	18	0.98	0.40		
RCMAX13	18	1.72	1.01		
RTMAX13	18	0.69	0.34		
RKE13	18	1.41	0.95		
RTHALF13	18	0.89	0.35		
RAUCT23	18	1.09	0.39		
RAUCI23	18	1.05	0.36		
RCMAX23	18	1.11	0.34		
RTMAX23	18	0.99	0.54		
RKE23	18	1.39	0.98		
RTHALF23	18	0.94	0.50		

VI. Dissolution

A. Formulation

The reference product contains selegiline HCl, lactose, citric acid, magnesium stearate and microcrystalline cellulose. The formulation of the test product is given in Table 47.

Table 47. Test Product Formulation

Ingredients	mg per Tablet
Selegiline HCl	5.0
Lactose, NF	
Corn Starch, NF	
Povidone, USP	
Talc, USP	
Magnesium Stearate, NF	
Total	150.0

B. Dissolution Testing

The sponsor submitted dissolution testing data by Pharmaceutical Forum method (p. 71448, March-April, 1994) and FDA suggested method. Both data for the test and reference products met the specifications. Dissolution data were summarized in Table 48.

PF method:

Medium: water, 500 mL
Temperature: 37°C
Apparatus: USP 2(paddle)
Rotation: 50 rpm
Specifications: NLT Q) in 30 min.

FDA method:

Medium: water, 500mL
Temperature: 37°C
Apparatus: USP 1(basket)
Rotation: 50 rpm
Specifications: NLT Q) in 20 min.

VII. Comments

1. Study under fasting conditions:

A total of 40 healthy male subjects participated in the study and Subject #20 was discontinued from the study before starting the 2nd period because of a positive alcohol screening. Thirty-nine subjects completed the fasting study.

A total of 29 subjects were used to analyze the plasma levels and pharmacokinetic parameters of selegiline. Thirty-eight subjects were used for amphetamine and 39 subjects were used for methamphetamine and desmethylselegiline.

Selegiline:

For 10 subjects the plasma levels were so low that meaningful profiles could not be obtained and the inter-subject variability was extremely high. The inter-subject variability at 0.5 hours was 205% CV and 173% CV for the test and reference products, respectively. The variability of the pharmacokinetic parameters was found to be very high reflecting the variability of the plasma levels.

The AUC's showed a CV of approximately 200% and 100% for the test and reference products, respectively. The Cmax also showed a similar magnitude of variability. The test/reference ratios for the AUC_t, AUC_i and C_{max} were 1.39, 1.41 and 1.06, respectively, for the non-transformed data and 0.96, 0.97 and 0.90 for the log-transformed data.

The 90% confidence intervals (CI) for the log-transformed AUC_t, AUC_i and C_{max} were 85-114, 84-110 and 78-107. The sponsor, however, reported a 90% CI of 82-115 for the log-transformed C_{max} by analyzing 38 subjects. The 90% CI for the log-transformed C_{max} does not meet the Division's requirement of 80-125%.

The test/reference ratios of pharmacokinetic parameters calculated for individuals showed a variability (CV) in the range of 100%, which is extremely high. In light of this, selegiline, the parent drug, may be excluded from the bioequivalence requirements for Selegiline Tablets.

Amphetamine:

Both the test and reference products showed similar plasma-time profiles. The peaks of the plasma amphetamine-time profiles were 2.66 ng/mL (%CV=25) and 2.60 ng/mL (%CV=20) occurred at 3 hours for the test and reference products, respectively.

The pharmacokinetic parameters, AUC_t, AUC_i and C_{max}, were comparable for both the test and reference products. Variability was also comparable and ranged 19-28% CV. The test/reference ratios were all within 0.94-0.99 for the log/non-transformed parameters. The 90% CI's for the log-transformed AUC_t, AUC_i and C_{max} were all within the 80-125% requirement.

Methamphetamine:

Both the test and reference products showed similar plasma-time profiles. The peaks of the plasma methamphetamine-time profiles were 10.64 ng/mL (%CV=17) and 10.94 ng/mL (%CV=16) occurred at 3 hours for the test product and at 2 hours for the reference product, respectively.

The pharmacokinetic parameters, AUC_t, AUC_i and C_{max}, were comparable for both the test and reference products. Variability was also comparable and ranged 16-26% CV. The test/reference ratios were all within 0.94-0.98 for the log/non-transformed parameters. The 90% CI's for the log-transformed AUC_t, AUC_i and C_{max} were all within the 80-125% requirement.

Desmethylselegiline:

Both the test and reference products showed similar plasma-time profiles. The peaks of the plasma desmethylselegiline-time profiles were 10.26 ng/mL (%CV=47) and 11.02 ng/mL (%CV=39) occurred at 0.75 hour for the test product and the reference product, respectively.

The pharmacokinetic parameters, AUC_t, AUC_i and C_{max}, were comparable for both the test and reference products. Variability was also comparable and ranged 38-46% CV. The test/reference ratios were all within 0.93-0.98 for the log/non-transformed parameters. The 90% CI's for the log-transformed AUC_t, AUC_i and C_{max} were all within the 80-125% requirement.

2. Study under nonfasting conditions:

A total of 20 healthy male subjects participated in the study and 18 subjects completed the nonfasting study. Subject #10 voluntarily withdrew from the study following Period 1 and Subject #16 was discontinued from the study during Period 1 due to illness (otitis media).

A total of 15 subjects were used to analyze the plasma levels and pharmacokinetic parameters of selegiline. Eighteen subjects were used for the three metabolites.

Selegiline:

The plasma selegiline levels under food conditions are much higher resulting in higher AUC and C_{max} as compared to the dosing under fasting conditions. The inter-subject variability is also extremely high for the plasma selegiline levels under fasting and food conditions. The peaks of the mean plasma levels were 390 pg/mL (%CV=77) at 0.75 hour for the test product under fasting conditions, 635 pg/mL (%CV=174) at 1 hour for the test product under food conditions, and 487 pg/mL (%CV=134) at 1.25 hours for the reference product under food conditions. It appears that there is a food effect with regard to the plasma selegiline level-time profiles.

The parameters under food conditions are as two-fold larger as the parameters under fasting conditions. The test/reference ratios under food conditions (RMEAN23) range 0.7-1.48 and do not meet the requirement by the Division.

Amphetamine:

All the three plasma amphetamine-time profiles, the test product under fasting conditions and the test and reference products under food conditions, were similar. The peaks of the plasma amphetamine-time profiles were 2.72 ng/mL (%CV=33) at 8 hours for the test product under fasting conditions, 2.75 ng/mL (%CV=29) at 4 hours for the test product under food conditions and 2.85 ng/mL (%CV=31) at 6 hours for the reference product under food conditions.

The pharmacokinetic parameters, AUC_t, AUC_i and C_{max}, were comparable for the three treatments. Variability was also comparable and ranged 30-50% CV. The test/reference ratios under food conditions (RMEAN23) were all within 0.89-1.04 for the log/non-transformed parameters and met the requirement of the Division.

Methamphetamine:

All the three treatments showed similar plasma-time profiles. The peaks of the plasma methamphetamine-time profiles were 9.99 ng/mL (%CV=19) at 3 hours for the test product under fasting conditions, 10.83 ng/mL (%CV=23) at 4 hours for the test product under food conditions and 10.03 ng/mL (%CV=24) at 4 hours for the reference product under food conditions.

The pharmacokinetic parameters, AUC_t, AUC_i and C_{max}, were comparable for the three treatments. Variability was also comparable and ranged 20-50% CV. The test/reference ratios under food conditions (RMEAN23) were all within 1.01-1.02 for

the log/non-transformed parameters and met the requirement of the Division.

Desmethylselegiline:

There were differences found among the three treatments in the plasma-time profiles. The peaks of the plasma desmethylselegiline-time profiles were 14 ng/mL (%CV=64) at 1 hour for the test product under fasting conditions, 8.33 ng/mL (%CV=36) at 1.5 hours for the test product under food conditions and 7 ng/mL (%CV=48) at 2 hours for the reference product under food conditions.

The pharmacokinetic parameters, AUC_t, AUC_i and C_{max}, were comparable for the test and reference products under food conditions. Variability was also comparable and ranged 28-59% CV. The test/reference ratios under food conditions (RMEAN23) were all within 1.01-1.07 for the log/non-transformed parameters and met the requirement of the Division.

3. Selegiline plasma levels and pharmacokinetic parameters under fasting and food conditions show high variabilities. Ten subjects under fasting conditions and three subjects under food conditions were removed from the data analysis due to insufficient plasma levels. It appears that 90% confidence limits for selegiline may not be a good indicator for the bioequivalence of Selegiline Tablets.

4. Assay validation is incomplete. The sponsor should also provide actual concentrations for the internal standard used in the recovery study.

5. In the fasting study, a total of 11 adverse events (paresthesia, dizziness, syncope, headache, rash, etc.) were reported by 9 subjects. All events (8 events for the test product and 3 events for the reference product) were not serious and no subjects were withdrawn from the study because of the adverse events.

   In the food study, a total of 26 adverse events (paresthesia, dizziness, syncope, headache, rash, etc.) were reported by 12 subjects. All events (14 events for the test product under fasting conditions, 6 events for the test product under food conditions and 6 events for the reference product under food conditions) were not serious and no subjects were withdrawn from the study because of the adverse events except Subject #16 who was discontinued from the study due to otitis media.

6. Dropouts: One dropout in the fasting study and two dropouts in the food study.

7. The sponsor submitted dissolution testing data by

Pharmaceutical Forum method (p. 71448, March-April, 1994) and FDA suggested method. Both data for the test and reference products met the specifications.

8. Formulation of the test product does not contain inactive ingredients which may hinder its bioavailability.

VIII. Deficiency

1. Concentrations of the internal standard under recovery data for the parent drug and metabolites should be identified.

2. Room temperature stability for metabolites: Storage time is missing.

3. Submitted C_{max} data on a PC diskette are different from the data in hard copy for amphetamine under food conditions.

4. Some of the SAS analysis output were compiled out of order and it causes difficulty reviewing. Care should be taken for future submissions.

5. For future submission of dissolution data, range (high and low) should be reported in addition to the mean, sd, and %CV.

IX. Recommendations

1. The *in vivo* bioequivalence studies conducted by Endo Laboratories under fasting and food conditions comparing its Selegiline Hydrochloride Tablets, 5 mg strength, to Somerset Pharmaceuticals' Eldepryl^{R} were found to be incomplete by the Division of Bioequivalence. The sponsor should respond to the comments under deficiencies.

2. The dissolution testing conducted by Endo Laboratories on its Selegiline Hydrochloride Tablets, 5 mg strength, Lot # **FE067A**, is acceptable.

The firm should be informed of the recommendations and deficiencies #1-5.

Moo Park, Ph.D.
Review Branch III
The Division of Bioequivalence

RD INITIALED RMHATRE
FT INITIALED RMHATRE for 8/31/95

Concur: N/A see memo 10/17/95 Date: _____

Keith Chan, Ph.D.
Director
Division of Bioequivalence

cc: ANDA #74-565 (original, duplicate), HFD-600 (Hare), HFD-630, HFD-344 (CViswanathan), HFD-658 (Mhatre, Park), Drug File, Division File

(Please select Typeover for Input.)

Table 48. In Vitro Dissolution Testing

Drug (Generic Name):Selegiline Hydrochloride Tablets
Dose Strength:5 mg
ANDA No.:73-138
Firm:Endo Laboratories
Submission Date:11/10/94
File Name:

I. Conditions for Dissolution Testing:PF method

USP 23 Basket: Paddle:x RPM: 50
No. Units Tested: 12
Medium:water Volume: 500 mL
Specifications:NLT) in 30 Min
Reference Drug: Somerset's Eldepryl[R] Tablets Lot #3Z011D
Assay Methodology·

Results of In Vitro Dissolution Testing:

Sampling Times (Minutes)	Test Product Lot # FE067A Strength(mg) 5			Reference Product Lot # 3Z011D Strength(mg)5		
	Mean %	Range	%CV	Mean %	Range	%CV
5	37.4		13.8	74.9		12.2
10	65.9		15.7	89.1		7.0
20	94.0		6.7	95.8		4.9
30	97.4		4.2	96.7		4.6

II. Conditions for Dissolution Testing:FDA proposed method

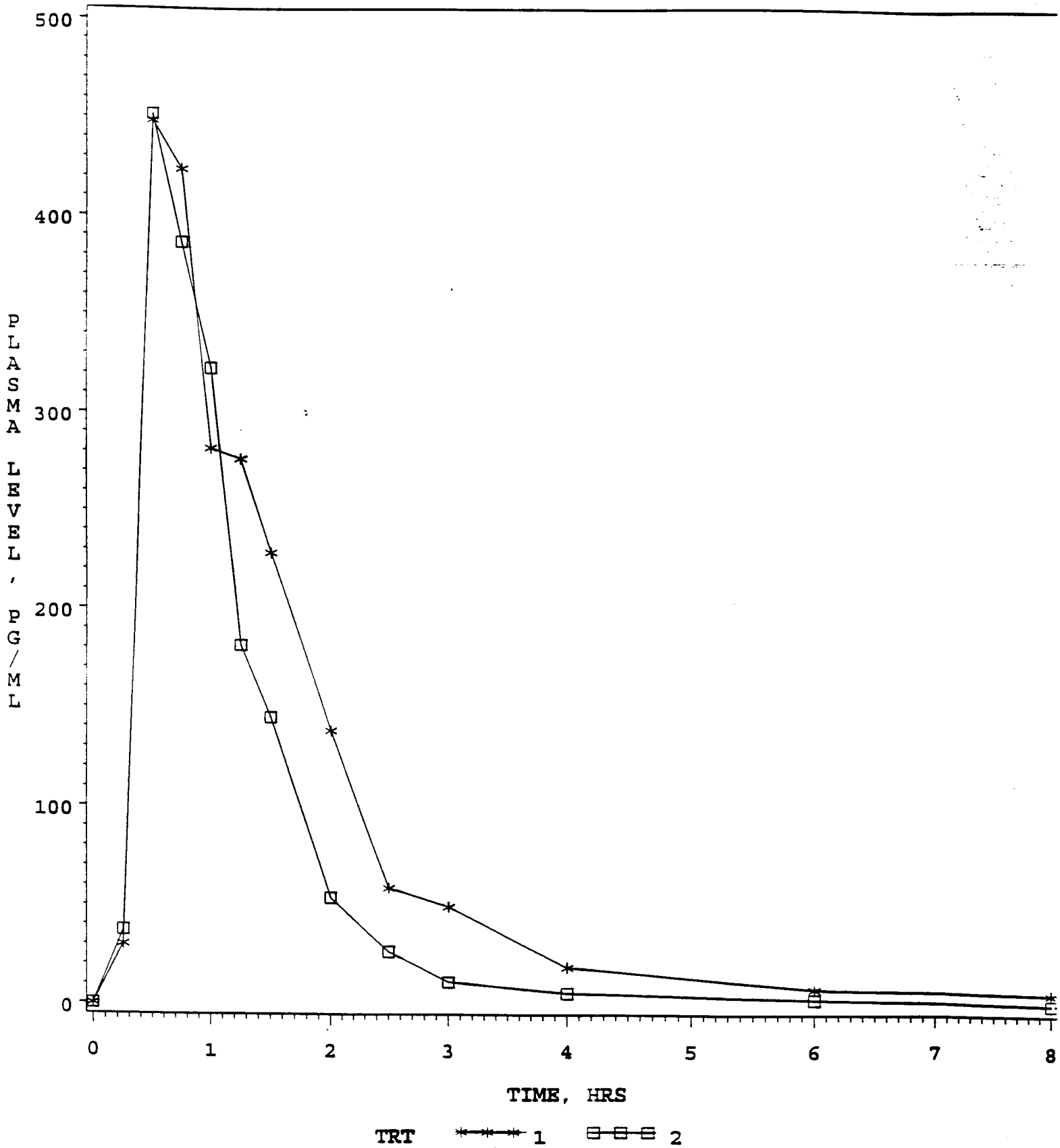
USP 23 Basket:x Paddle: RPM: 50
No. Units Tested: 12
Medium:water Volume: 500 mL
Specifications:NLT in 30 Min
Reference Drug: Somerset's Eldepryl[R] Tablets Lot #3Z011D
Assay Methodology·

Results of In Vitro Dissolution Testing:

Sampling Times (Minutes)	Test Product Lot # FE067A Strength(mg) 5			Reference Product Lot # 3Z011D Strength(mg) 5		
	Mean %	Range	%CV	Mean %	Range	%CV
5	40.8		14.8	66.4		17.8
10	64.4		8.7	85.9		5.0
20	94.9		2.4	94.3		3.1
30	93.5		4.2	93.8		3.5

FIG 1. PLASMA SELEGILINE LEVELS

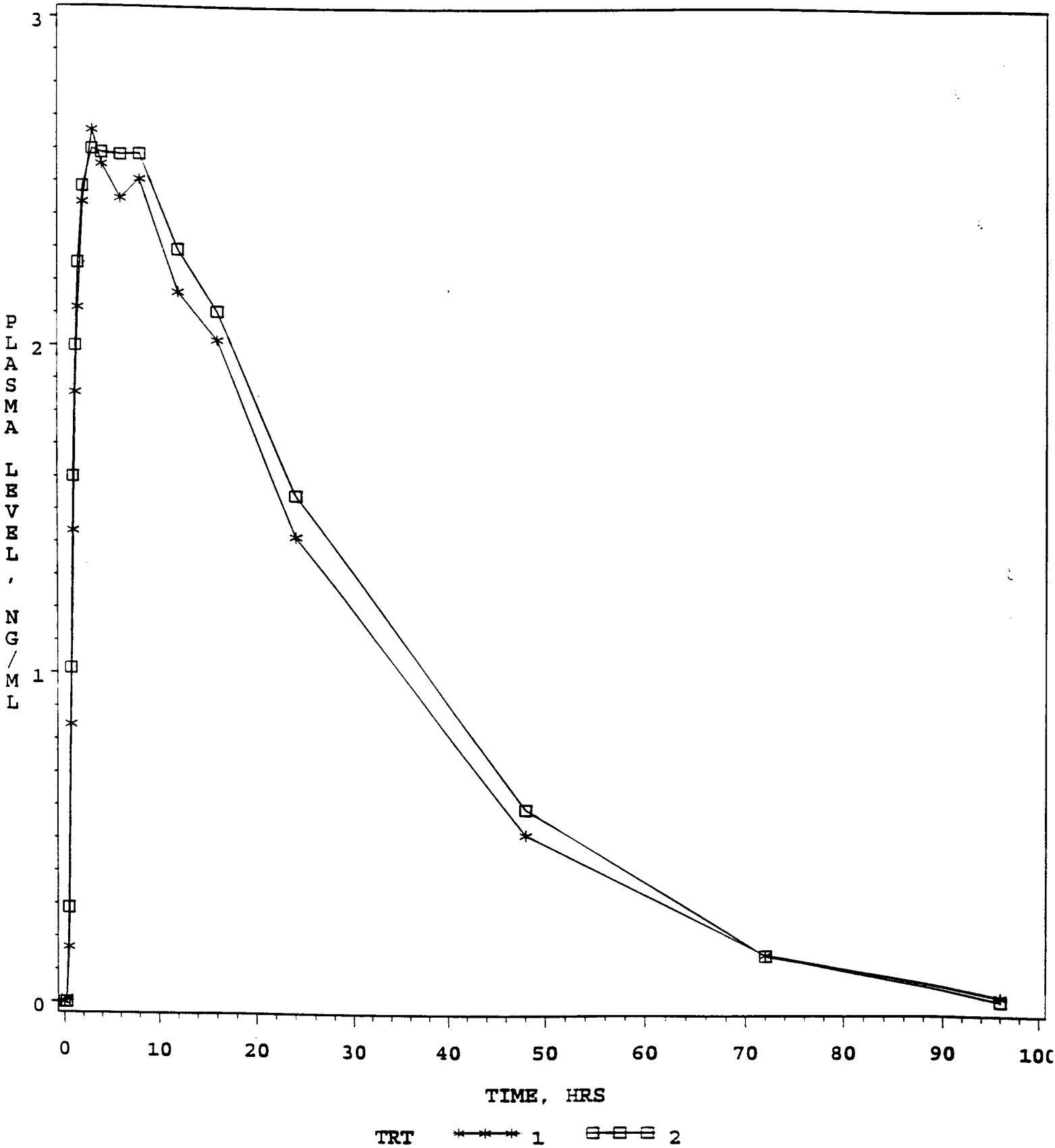
SELEGILINE HCl TABLETS, 5 MG, ANDA #74-565
UNDER FASTING CONDITIONS
DOSE=2 X 5 MG



1=TEST PRODUCT(ENDO) 2=REFERENCE PRODUCT(SOMERSET)

FIG 2. PLASMA AMPHETAMINE LEVELS

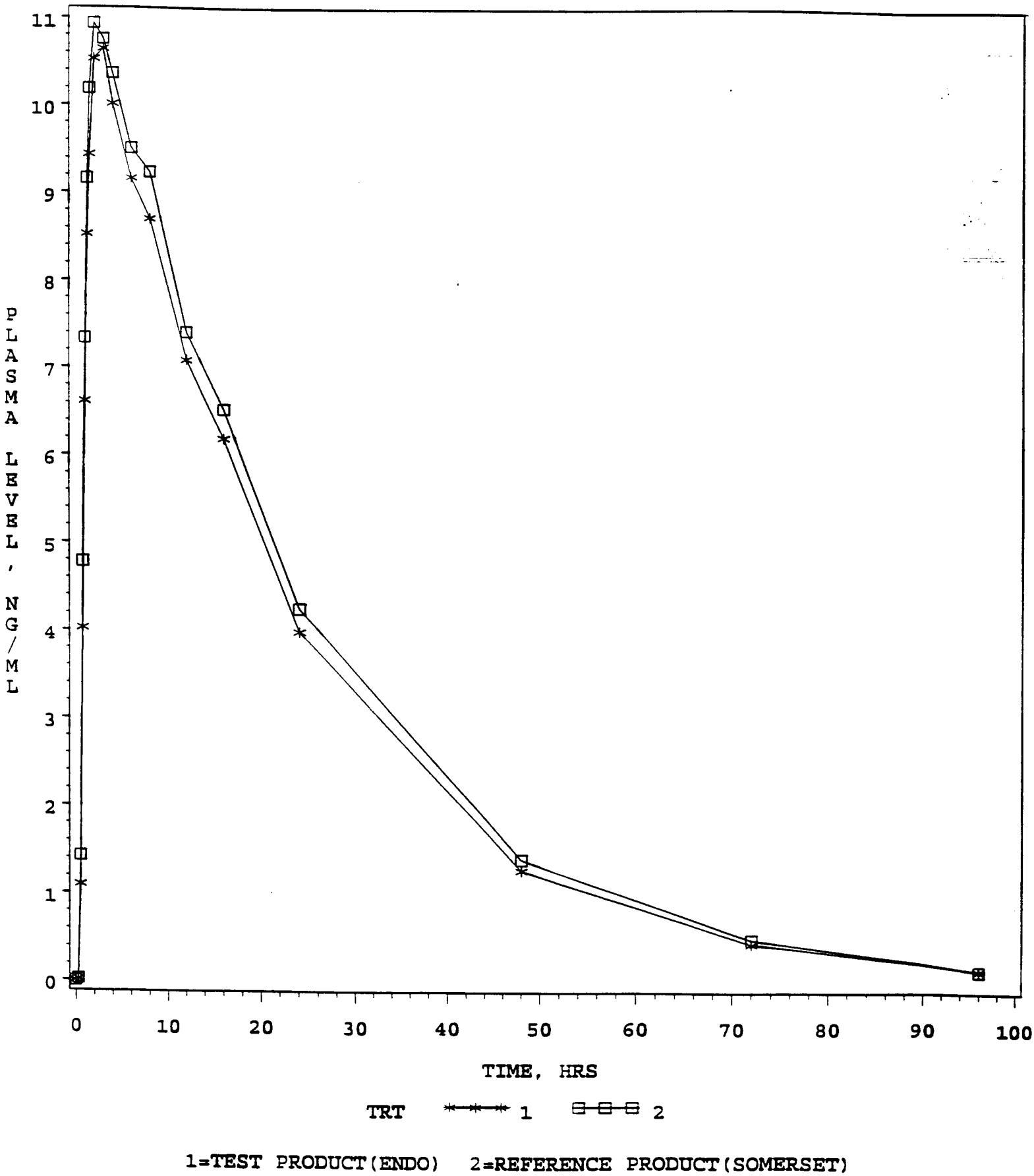
SELEGILINE HCl TABLETS, 5 MG, ANDA #74-565
UNDER FASTING CONDITIONS
DOSE=2 X 5 MG



1=TEST PRODUCT(ENDO) 2=REFERENCE PRODUCT(SOMERSET)

FIG. 3: PLASMA METHAMPHETAMINE LEVELS

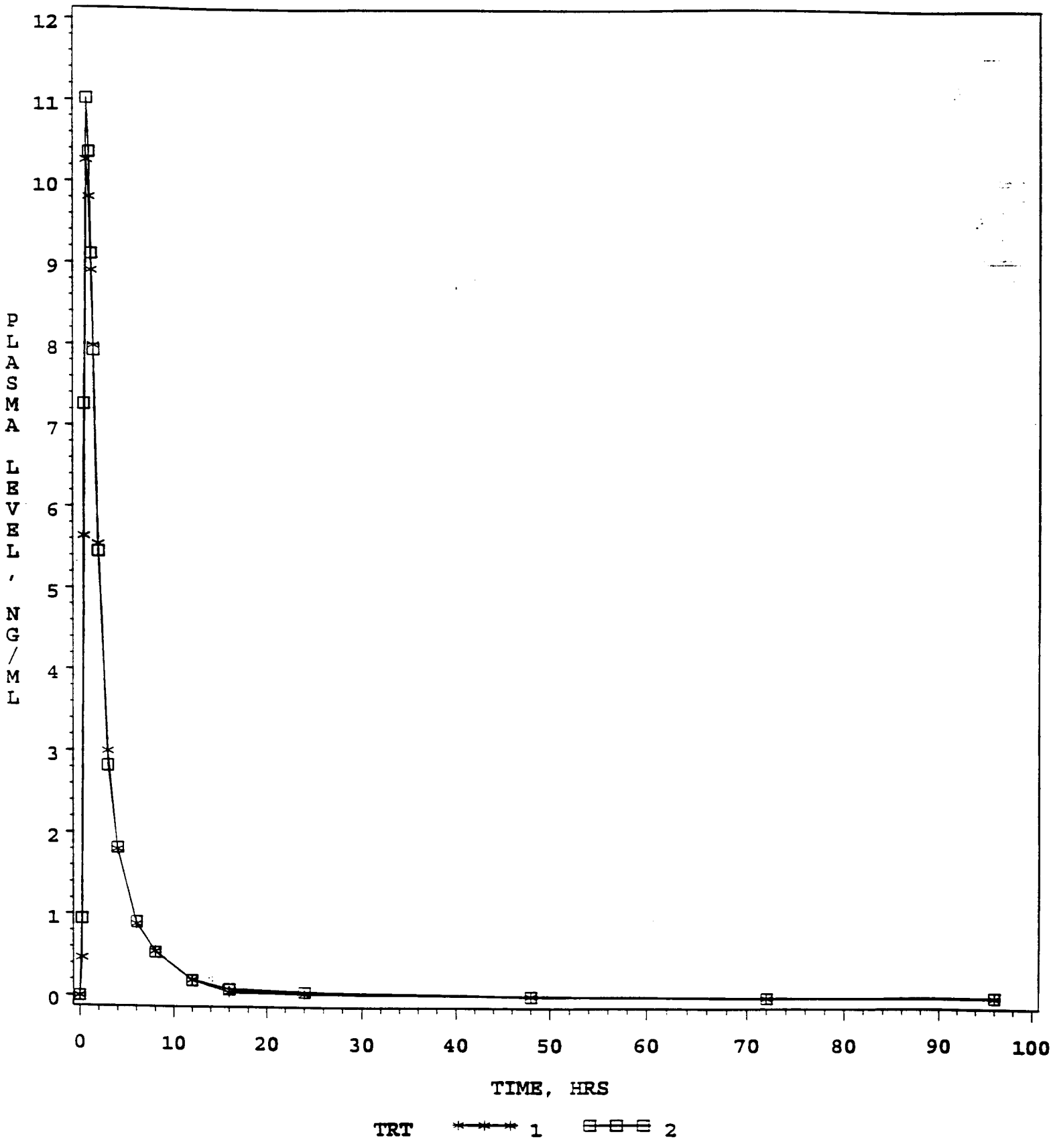
SELEGILINE HCl TABLETS, 5 MG, ANDA #74-565
UNDER FASTING CONDITIONS
DOSE=2 X 5 MG



1=TEST PRODUCT(ENDO) 2=REFERENCE PRODUCT(SOMERSET)

FIG 4. PLASMA DESMETHYLSELEGILINE LEVELS

SELEGILINE HCl TABLETS, 5 MG, ANDA #74-565
UNDER FASTING CONDITIONS
DOSE=2 X 5 MG



1=TEST PRODUCT(ENDO) 2=REFERENCE PRODUCT(SOMERSET)

FIG 5: PLASMA SELEGILINE LEVELS

SELEGILINE HCl TABLETS, 5 MG, ANDA #74-565
UNDER FED CONDITIONS
DOSE=2 X 5 MG

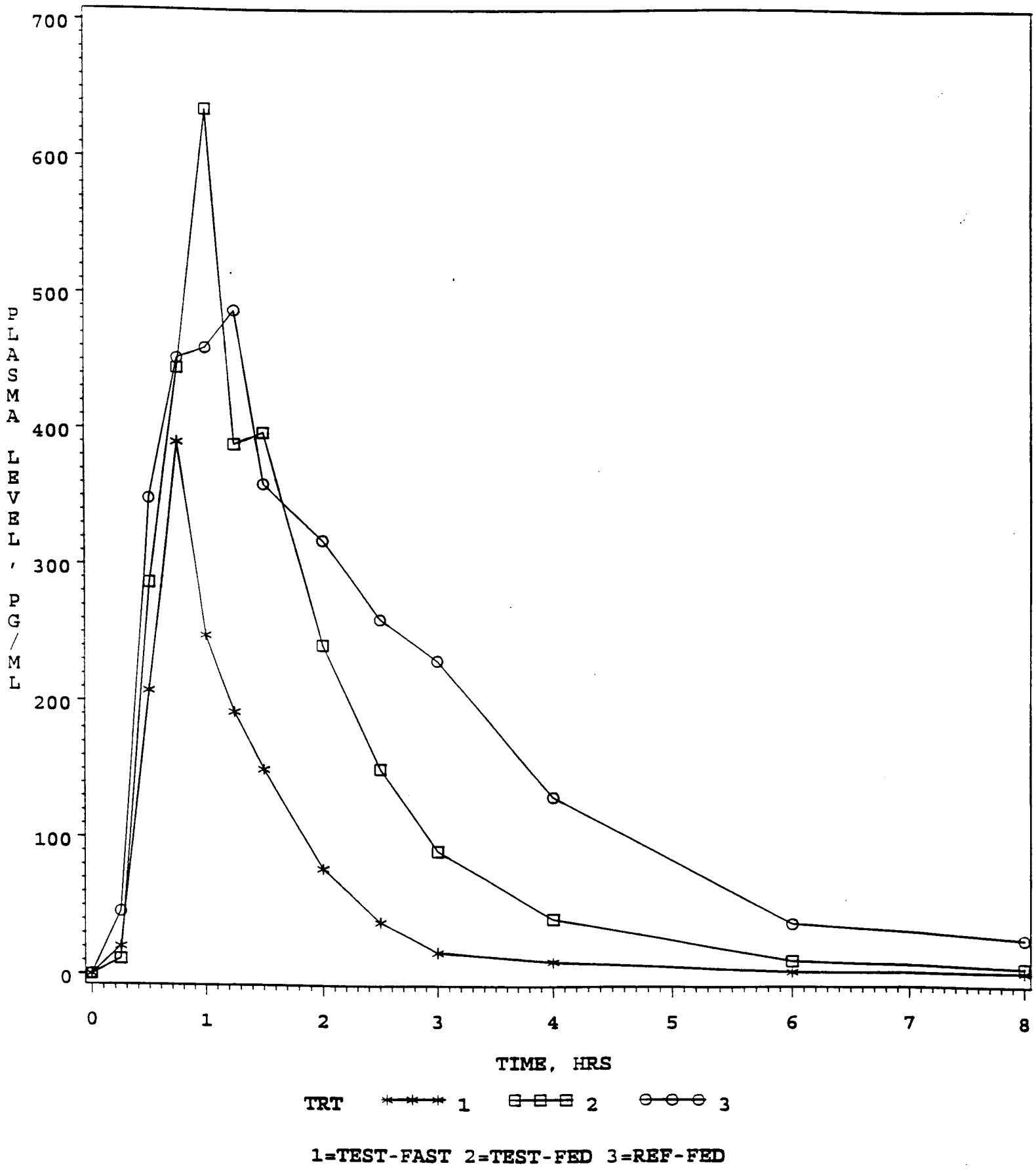


FIG 6. PLASMA AMPHETAMINE LEVELS

SELEGILINE HCl TABLETS, 5 MG, ANDA #74-565
UNDER FED CONDITIONS
DOSE=2 X 5 MG

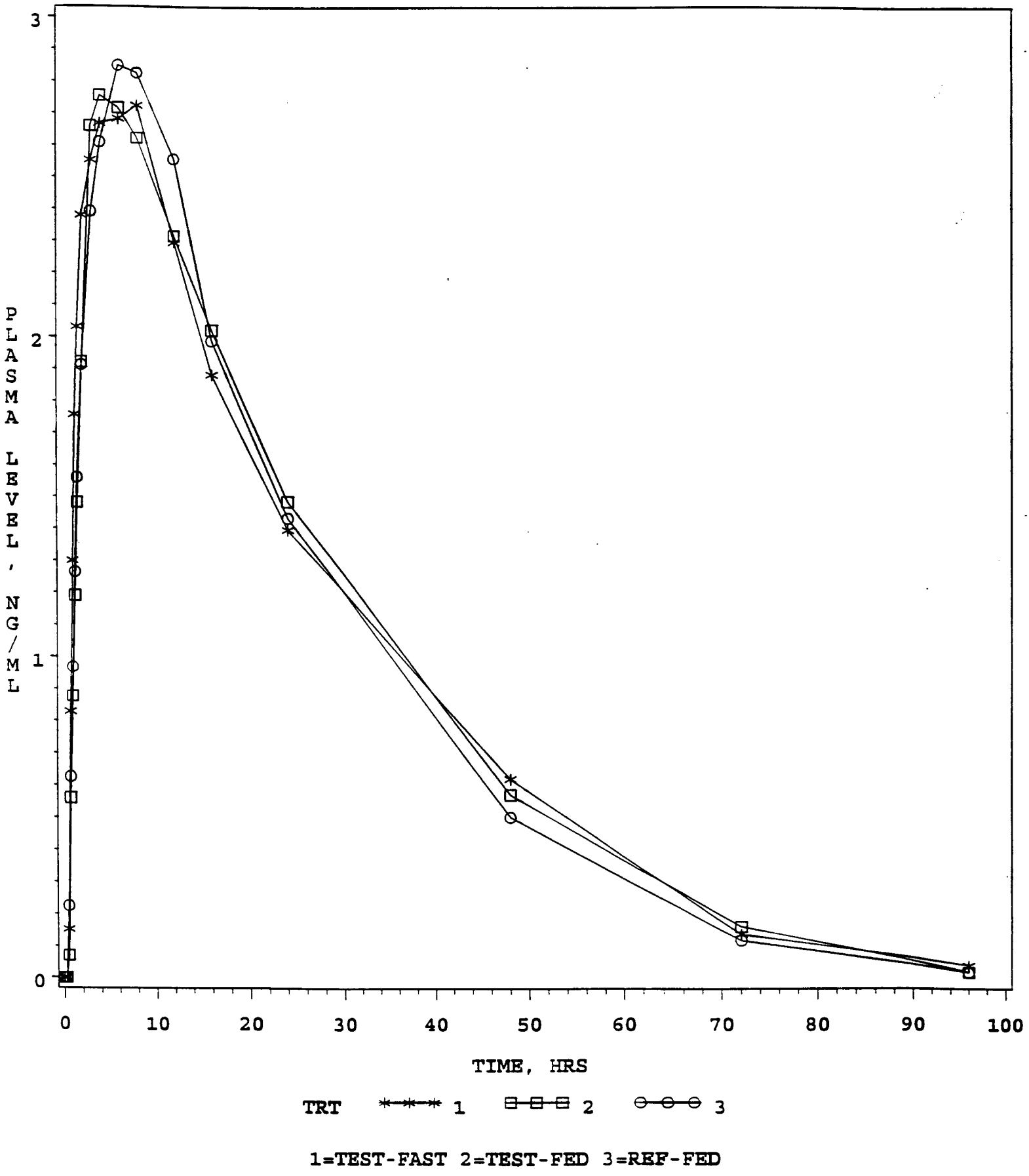


FIG 7: PLASMA METHAMPHETAMINE LEVELS

SELEGILINE HCl TABLETS, 5 MG, ANDA #74-565
UNDER FED CONDITIONS
DOSE=2 X 5 MG

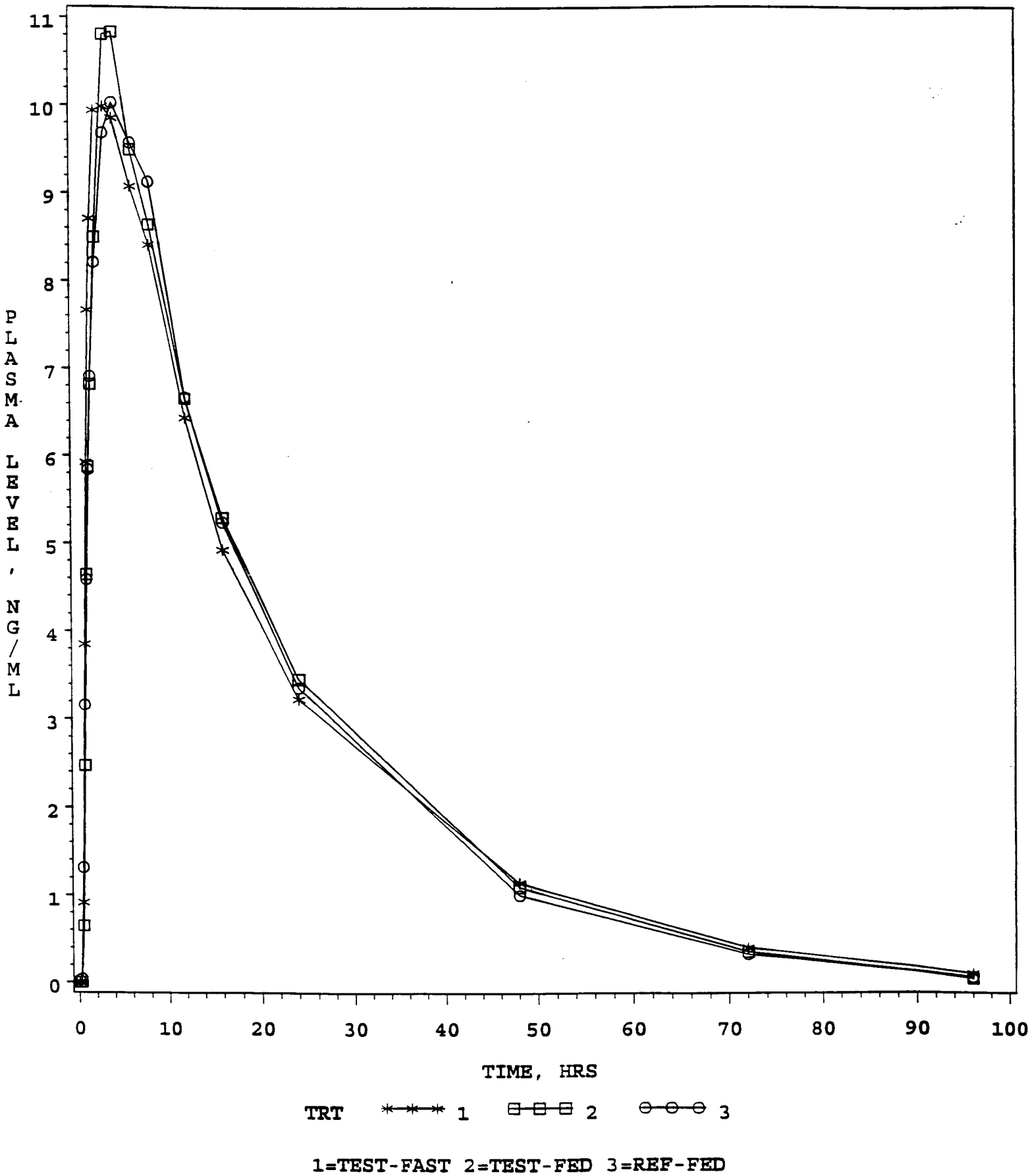


FIG 8. PLASMA DESMETHYLSELEGILINE LEVELS

SELEGILINE HCl TABLETS, 5 MG, ANDA #74-565
UNDER FED CONDITIONS
DOSE=2 X 5 MG